WASHINGTON NEWS

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PHYSICIANS' COOPERATION CITED AT DRUG HEARINGS

The role of the American Medical Association in cooperating with congressional investigations of the drug industry and A. M. A. standards on drug advertising were both challenged and defended at the current Senate inquiry on drug prices.

Although most of the testimony at the sessions of the Senate anti-trust subcommittee headed by Sen. Estes Kefauver (D., Tenn.) dealt with drug prices, there was some discussion of advertising and the A. M. A.

The most controversial charge was leveled by Rep. John Blatnik (D., Minn.), who led a House government operations subcommittee investigation of drugs two years ago. Mr. Blatnik, testifying before the Senate group, contended that the A. M. A.'s attitude was "[illegible]." In a press release he said medical [illegible]" the probe "at every turn."

In reply, the A. M. A. issued a statement asserting that the charge was "completely untrue."

The statement continued, "A representative of the A. M. A. testified before the subcommittee. In all of the subcommittee hearings the A. M. A. cooperated fully. Correspondence in our files documents this cooperation in the form of thank-you letters from Congressman Blatnik and staff. The A. M. A. has been fighting false and misleading drug advertisements for over 50 years, long before the government operations subcommittee even existed."

Senator Kefauver made it clear that as far as the present investigation was concerned he did not share Representative Blatnik's views. The A. M. A. has "cooperated fully," he said, adding that the organization should be congratulated on its aims and objectives which include "fair advertising and the best medication for the people of the United States."

The senator said he wanted to "make it very clear" that the subcommittee's relations with the A. M. A. have been "very pleasant," that there had been no difficulty at all in such dealings, and that the organization and physicians across the country have "exhibited extreme interest" in the subcommittee's goals.

Although Blatnik had critical words for the medical profession, he departed from his prepared statement to make this assertion:

"It is not made quite clear in this summary statement, but there is some very fine work done within the medical profession itself. Practically all, certainly most of the professional journals screen the advertising which they accept. Some even have medical boards that will process and screen all advertising of so-called ethical drugs and will accept only a high-grade type of advertising as a degree of modesty with their claims and yet accuracy, advertising bona fide legitimate, well-established and recognized ethical drugs."

The hearings thus far have concentrated on makers of steroid drugs and tranquilizers. In February, the subcommittee was slated to call Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association, and other witnesses to testify on the general subject of drug prices. Kefauver has maintained that the prices are too high, but industry witnesses have pointed out the high risks of the business, the large sums needed for research, and the comparatively recent growth of the ethical drug industry since World War II.

ADMINISTRATION STUDYING SOCIAL SECURITY EXPANSION

President Eisenhower said, at his weekly news conference, that the administration has under consideration a plan to boost social security benefits for elderly beneficiaries. However, the Chief Executive emphasized, "There has been no conclusion reached in the administration; I have not yet made any recommendation on it."

A reporter, noting that "there seems to be considerable pressure in Congress for amending the Social Security Act this year," asked if the administration is planning to propose any changes.

Mr. Eisenhower replied, "Well, there is under. . . . there is under consideration a possible change to run up the taxes by a quarter of 1% to take greater care, make greater provision for the care of the aged."

This would be the same increase called for in the Forand proposal to broaden the social security system to provide for some federal financing of health care for the beneficiaries, a bill that opponents assert would be the first step toward complete government control of medicine.

Mr. Eisenhower did not indicate what type of "care" was involved in the proposal being studied in high administration circles. Arthur S. Flemming, Secretary of Health, Education, and Welfare, has promised that the administration would come up this year with a "positive" program for helping the elderly meet their medical and health bills.

Meanwhile, backers of the controversial Forand legislation have pressed their drive for congressional enactment. The AFL-CIO, prime proponents of the bill that was vigorously opposed by the administration, urged a letter-writing campaign b all members of the federation to the congressm who make up the House Ways and Means Comr tee that has original jurisdiction over the mea

SENATE URGED TO KEEP LABELING BILL STRONG

The American Medical Association asked the Senate Commerce Committee to reject recommendations to weaken the measure calling for precautionary labeling of household substances that might cause harm if consumed or ignited.

In a letter to the Committee, Dr. F. J. L. Blasingame, A. M. A. Executive Vice-president, opposed a suggestion to omit toxicological tests in determining the necessity of the signal word "danger" and to apply the term only to highly toxic substances which would also be labelled "poison."

This would "seriously dilute the effectiveness of the proposed legislation," said Dr. Blasingame. "The American Medical Association does not believe that these recommendations are sound. Objection to toxicity standards, because they overtax testing facilities, is a recurring but unfounded fear. This fear has been expressed during the consideration of every legislative improvement in the regulation of chemicals" since 1927, said Dr. Blasingame. "Admittedly, the provisions of S. 1283 [the labeling bill] would require more toxicity testing than has heretofore been undertaken for these products. However, improved protection for consumers against bodily injury necessitates and justifies the additional work. In addition, experience with older laws indicates that the economics of the problem will insure facilities and personnel to meet the demand. We strongly recommend maintaining the toxicity standards for 'danger' set forth in S. 1283. . . ."

The A. M. A. official also objected to a proposal to limit the scope of the measure to substances "suitable for household use," rather than "distributed as packaged chemicals for nonmanufacturing purposes." This would cause the same "inherent weakness" now found in the Federal Caustic Poisons Act, and "to continue it under the guise of new and improved legislation is hardly a step forward and certainly will not meet the compelling need for better control of hazardous substances," said Dr. Blasingame.

The measure before the Committee, headed by Sen. Warren Magnuson (D., Wash.), would replace existing statutes and provide broader coverage of products requiring labeling as well as more detailed labeling requirements. Since the present federal labeling law was enacted in 1927 for poisonous substances, many new compounds for household, commercial, and industrial use have been introduced which are not covered.

BROADER MEDICAL SCHOOL GRANTS ASKED

Arthur C. Flemming, Secretary of Health, Education, and Welfare, proposed legislation to provide broader grants to medical, dental, and public health schools for medical and health-related research and research training programs.

In letters to the President of the Senate and the peaker of the House, Flemming asked that the blic Health Service Act be amended to give .U. S. Surgeon General authority to make grants he general support of the research programs of institutions, as well as the grants now authorized to support specific projects proposed by individual applicants.

Funds for the general grants would come from a uniform percentage, not to exceed 15%, of the appropriations to the National Institutes of Health for research grants authorized in existing legislation.

"The establishment of a program of institutional research grants which would be possible under this legislation will carry into effect recommendations made to the HEW Secretary by a distinguished group of consultants who have studied problems of medical research and education under the chairmanship of Dr. Stanhope Bayne-Jones," Flemming said.

The Bayne-Jones committee has said, "An increase in the capacity of research and educational institutions to perform their educational and research functions more effectively would be in the national interest. To this end, federal funds for research should be provided under conditions which give the institutions a substantial degree of freedom in deciding how to use the funds."

President Eisenhower's Science Advisory Committee also recommended that "institutional grants for specialized fields is another instrumentality [in addition to project grants and program grants] that should be encouraged" in providing support of government-sponsored research in nongovernmental installations.

Flemming pointed out that funds made available for the support of research projects by the National Institutes of Health have risen from a level of $3,500,000 in fiscal year 1947 to a total of 200 million dollars in fiscal year 1960. These funds have been in the form of support for specific projects proposed by individual research investigators working in research laboratories, hospitals, medical schools, and other institutions.

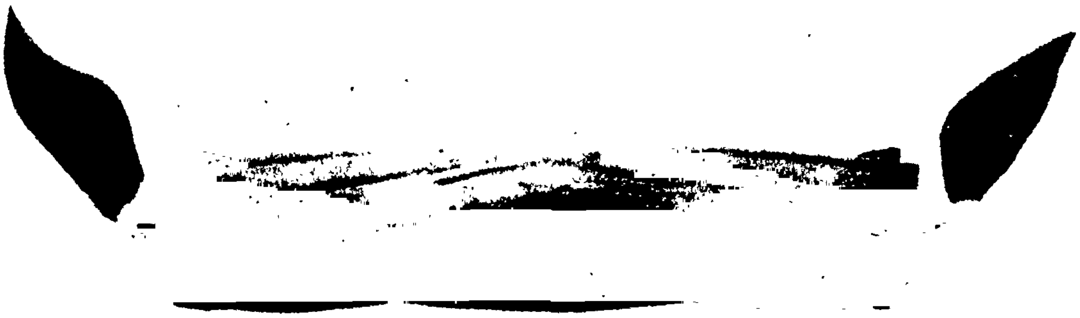
"In large part, the support of research exclusively through the project system has deprived educational institutions of a large measure of autonomy and freedom in determining the character and direction of their research activities," Flemming said. "Furthermore, exclusive reliance on the project system does not make it possible for educational institutions to assume a position of responsibility in carrying out their role in the conduct of medical and health-related research supported through federal funds."

MISCELLANY

The number of resident patients in federal mental hospitals dropped for the fourth consecutive year in 1959. The 542,721 patients in 277 mental hospitals at the end of the year was 2,142 less than in 1958. Dr. Robert H. Felix, director of the National Institute of Mental Health, credited the decline to improved treatment, a basic change in the philosophy of hospital administration and treatment, and a change in the public attitude toward mental illness.

The U. S. Bureau of Narcotics reported there were 45,391 active drug addicts in the United States as of Jan. 1, with the state of New York leading the country with 20,732 addicts. California was second with 6,471 addicts, and Illinois was third with 6,191 addicts.

When the vagus burns at both ends



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The slow simmer of anxiety frequently causes kindred gastrointestinal overactivity. The spasticity and the accompanying distress of excess acid lead to loss of efficiency. Patients subject to such psychoenteric upsets require therapy to calm both ends of the vagus.

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Pro-Banthīne with Dartal contains 15 mg. of Pro-Banthīne (brand of propantheline bromide) and 5 mg. of Dartal (brand of thiopropazate dihydrochloride) in each tablet.

Dosage: One tablet three times a day.

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Research in the Service of Medicine.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.
1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 2.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-Dec. 1.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 25-30.

AMERICAN

1960

February

Alaska State Medical Association, Anchorage, Feb. 18-20. Dr. George Hale, 501 "L" Street, Anchorage, Alaska, Chairman.

American Academy of Occupational Medicine, Williamsburg Inn, Williamsburg, Va., Feb. 11-13. Capt. Lloyd B. Shone, Bureau of Medicine and Surgery, Navy Dept., Washington 25, D. C., Secretary.

American College of Allergists, Inc., Americana Hotel, Bal Harbour, Miami Beach, Fla., Feb. 28-Mar. 5. Mr. Eloi Bauers, 2160 Rand Tower, Minneapolis 2, Executive Vice-President.

American College of Surgeons, North Carolina Chapter, Hotel Barringer, Charlotte, N. C., Feb. 26-27. For information write Dr. Alexander Webb Jr., 201 Bryan Bldg., Cameron Village, Raleigh, N. C.

American College of Surgeons, Sectional Meeting for Surgeons and Nurses, Statler Hilton, Boston, Feb. 29-Mar. 3. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Orthopsychiatric Association, Inc., Sherman Hotel, Chicago, Feb. 25-27. Marion F. Langer, Ph.D., 1790 Broadway, New York 19, Executive Secretary.

Arizona Academy of General Practitioners and Arizona Psychiatric Association Psychiatric Seminar, Phoenix, Ariz., Feb. 13-14. Dr. James L. Grobe, 5630 N. 27th Ave., Phoenix, Ariz., Chairman.

California Medical Association, Ambassador Hotel, Los Angeles, Feb. 21-24. Mr. John Hunton, 450 Sutter St., San Francisco 8, Executive Secretary.

Central Surgical Association, Drake Hotel, Chicago, Feb. 18-20. Dr. Angus D. McLachlin, Victoria Hospital, London, Ont., Canada, Secretary.

National Association of Methodist Hospitals and Homes, Deshler Hilton Hotel, Columbus, Ohio, Feb. 16-18. Mr. Olin E. Oeschger, 740 Rush St., Chicago 11, General Secretary.

Society of University Surgeons, Minneapolis, Feb. 11-13. Dr. Ben Eiseman, 4200 E. Ninth Ave., Denver 20, Secretary.

Symposium on Fundamental Cancer Research (14th), University of Texas, Houston, Feb. 25-27. For information write: University of Texas M. D. Anderson Hospital & Tumor Institute, Houston 25, Texas.

March

American Broncho-Esophagological Association, Deauville Hotel, Miami Beach, Fla., Mar. 15-16. Dr. F. Johnson Putney, 1712 Locust St., Philadelphia 3, Secretary.

American Academy of Forensic Sciences, Drake Hotel, Chicago, Mar. 3-5. Dr. W. J. R. Camp, 1853 W. Polk St., Chicago 12, Secretary-Treasurer.

American Academy of General Practice, Philadelphia, Mar. 18-24. Mr. Mac F. Cahal, Volker Blvd., at Brookside, Kansas City 12, Mo., Executive Director.

American Association for the History of Medicine, Inc., Charleston, S. C., Mar. 24-26. John B. Blake, Ph.D., c/o Smithsonian Institution, Washington 25, D. C., Secretary.

American College of Surgeons, Sectional Meeting, The Broadmoor, Colorado Springs, Colo., Mar. 21-23. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Sheraton-Portland Hotel, Portland, Ore., Mar. 28-30. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Gastroenterological Association, Roosevelt Hotel, New Orleans, Mar. 31-Apr. 2. Dr. Wade Volwiler, Dept. of Med., Univ. of Washington, Seattle, Secretary.

American Gastroscopic Society, Roosevelt Hotel, New Orleans, Mar. 30. Dr. Arthur M. Olsen, Mayo Clinic, Rochester, Minn., Secretary-Treasurer.

American Laryngological Association, Deauville Hotel, Miami Beach, Fla., Mar. 18-19. Dr. Lyman Richards, Massachusetts Institute of Technology, Cambridge 39, Mass., Secretary.

American Laryngological, Rhinological and Otological Society, Inc., Deauville Hotel, Miami Beach, Fla., Mar. 15-17. Dr. C. Stewart Nash, 708 Medical Arts Bldg., Rochester 7, N. Y., Secretary.

American Otological Society, Deauville Hotel, Miami Beach, Fla., Mar. 13-14. Dr. Lawrence R. Boies, University Hospital, Minneapolis 14, Minn., Executive Secretary-Treasurer.

American Otorhinologic Society for Plastic Surgery, Inc., Deauville Hotel, Miami Beach, Fla., Mar. 6-13. Dr. Joseph G. Gilbert, 75 Barberry Lane, Roslyn Heights, N. Y., Secretary.

American Psychosomatic Society, Sheraton-Mount Royal Hotel, Montreal, Mar. 26-27. Miss Joan K. Erpf, 265 Nassau Rd., Roosevelt, N. Y., Executive Assistant.

American Radium Society, Caribe Hilton Hotel, San Juan, Puerto Rico, Mar. 17-19. Dr. Robert L. Brown, Robert Winship Clinic, Emory University, Atlanta 22, Ga., Secretary.

Association of Clinical Scientists, DeWitt Clinton Hotel, Albany, N. Y., March 3-5. Dr. Robert P. MacFate, 54 W. Hubbard St., Chicago 10, Secretary.

Intermountain Pediatric Society, Stardust Hotel, Las Vegas, Nev., Mar. 28-29. Dr. Joseph R. Newton, 2000 S. 9th East, Salt Lake City, Utah, Publicity Chairman.

Missouri State Medical Association, Sheraton-Jefferson Hotel, St. Louis, Mar. 13-16. Mr. T. R. O'Brien, 634 N. Grand Blvd., St. Louis 3, Executive Secretary.

National Health Council, National Health Forum, Miami, Fla., Mar. 13-18. Mr. Philip E. Ryan, 1790 Broadway, New York 19, Executive Director.

National Multiple Sclerosis Society, New York City, Mar. 8. Mr. Donald Vail, 257 Fourth Ave., New York 10, Secretary.

Neurosurgical Society of America, Del Monte Lodge, Calif., Mar. 30-Apr. 2. Dr. Raymond K. Thompson, 803 Cathedral St., Baltimore 1, Secretary.

New Orleans Graduate Medical Assembly, Roosevelt Hotel, New Orleans, Mar. 7-10. Miss Irma B. Sherwood, 1430 Tulane Ave., New Orleans 12, Executive Secretary.

Southeastern Surgical Congress, Roosevelt Hotel, New Orleans, Mar. 21-24. Dr. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga., Executive Secretary.

Southwestern Society for Nuclear Medicine, Menger Hotel, San Antonio, Texas, Mar. 26-27. Dr. N. T. Werthessen, Southwest Foundation for Research and Education, R. R. 4, Box 86, San Antonio 7, Texas, Program Chairman.

Southwestern Surgical Congress, Riviera Hotel, Las Vegas, Nev., Mar. 28-31. Miss Mary O'Leary, 1213 Medical Arts Bldg., Oklahoma City, Okla., Executive Secretary.

April

Alabama, Medical Association of the State of, Admiral Semmes Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery 4, Executive Secretary.

American Academy of Neurology, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

American Association for the Advancement of Science, Section on Medical Sciences, Vanderbilt University, Apr. 18-19. Dr. George R. Meneely, Vanderbilt University School of Medicine, Nashville 5, Tenn., Chairman.

American Association of Anatomists, Statler-Hilton, New York City, Apr. 11-16. Dr. Louis B. Flexner, Dept. of Anatomy, School of Medicine, Univ. of Pa., Philadelphia 4, Secretary-Treasurer.

American Association of Immunologists, Chicago, Apr. 11-15. Dr. Calderon Howe, Columbia Univ. College of Physicians and Surgeons, New York 22, Secretary-Treasurer.

American Association of Pathologists and Bacteriologists, Hotel Peabody, Memphis, Tenn., Apr. 28-30. Dr. Russell L. Holman, Dept. of Pathology, L. S. U. School of Medicine, New Orleans, La., Secretary.

American Association of Railway Surgeons, Drake Hotel, Chicago, Apr. 7-9. Mr. Chester C. Guy, 5800 Stony Island Ave., Chicago 37, Executive Secretary.

American College Health Association, Toronto, Canada, Apr. 27-30. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary Treasurer.

American College of Obstetricians and Gynecologists, Netherland Hilton Hotel, Cincinnati, Apr. 2-6. Mr. Donald F. Richardson, 79 W. Monroe St., Chicago 3, Executive Secretary.

American College of Physicians, Mark Hopkins & Fairmont, San Francisco, Apr. 4-9. Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Executive Secretary.

American College of Surgeons, Sectional Meeting, Hotel Leamington, Minneapolis, Apr. 11-13. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Kahler Hotel, Rochester, Minn., Apr. 14. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, West Virginia Chapter, The Greenbrier, White Sulphur Springs, W. Va., Apr. 1-2. Dr. Ray E. Burger, Grace Hospital, Welch, W. Va., Vice-President.

American Dermatological Association, Inc., Boca Raton Hotel, Boca Raton, Fla., Apr. 8-12. Dr. Wiley M. Sams, 308 Ingraham Bldg., Miami 32, Fla., Secretary.

American Physiological Society, Chicago, Apr. 11-15. Ray G. Daggs, D.Sc., 9650 Wisconsin Ave., Washington 14, D. C., Executive Secretary.

American Proctologic Society, Shamrock Hilton Hotel, Houston, Texas, Apr. 25-27. Dr. Norman D. Nigro, 10 Peterboro, Detroit 1, Secretary.

American Public Health Association, Southern Branch, Memphis, Tenn., Apr. 13-15. Dr. L. M. Graves, Shelby County Health Department, Memphis, Tenn., Chairman, Local Arrangements, Committee.

American Society for Artificial Internal Organs, Pick-Congress Hotel, Chicago, Apr. 10-11. Dr. Charles K. Kirby, 3400 Spruce St., Philadelphia 4.

American Society of Biological Chemists, Inc., Chicago, Apr. 11-[illegible]. Dr. Frank W. Putnam, Dept. of Biochemistry, Univ. of Florida, Gainesville, Secretary.

American Society for Experimental Pathology, Pick Congress Hotel, Chicago, Apr. 11-15. Dr. J. F. A. McManus, Univ. of Alabama Med. Center, Birmingham, Ala., Executive Secretary.

American Society of Facial Plastic Surgery, Hotel Elysee, New York City, Apr. 6. Dr. Samuel M. Bloom, 123 E. 83d St., New York 28, Secretary.

American Society of Internal Medicine, Sheraton-Palace Hotel, San Francisco, Apr. 1-3. Mr. Robert L. Richards, 350 Post St., San Francisco 8, Executive Director.

American Society for Pharmacology and Experimental Therapeutics, Inc., Chicago, Apr. Dr. Karl H. Beyer Jr., Merck Sharp and Dohme Research Labs., West Point, Pa., Secretary.

American Society for the Study of Sterility, Sheraton-Gibson Hotel, Cincinnati, Apr. 1-3. Dr. Herbert H. Thomas, 920 S. 19th St., Birmingham 5, Ala., Executive Secretary.

American Surgical Association, The Greenbrier, White Sulphur Springs, W. Va., Apr. 3-6. Dr. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Secretary.

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CURIOSITY, CULTURE, AND CURRICULA

William Dock, M.D., Brooklyn, New York

WHEN Chaucer described the doctor who rode with his pilgrims to Canterbury, he credited the "parfit pratisour" with knowing the works on medicine of many Greek, Latin, Arabic, French, and British authors. But he added drily: "His studie was but litel on the bible." In the ensuing 600 years there has been much comment about the physician's lack of interest in "the noblest monument of English prose." The esthetic as well as the ethical attitudes of our culture are based on the Bible, and it may well cause concern that a profession with high social status and authority over the bodies and minds of men should have impressed so many acute observers as being unconcerned about culture and religion.

Location of Medical Schools

In the past year two medical schools of great repute, Johns Hopkins and Leland Stanford Jr., have implemented long-considered plans to do something about this situation. As was stated at the dedication of the new medical center in Palo Alto, the decision to move from San Francisco and from the long-established center with facilities for research and one of the best library buildings of any medical school in the world was based on the "desire to encourage concurrent study of the arts, literature, history, religion, politics—in other words, the humanities and social sciences—during all the years the medical student is preparing to accept the responsibilities of being a doctor."

In choosing locations for new medical schools the relative advantages of large cities as against university communities must be considered. A medical student on a university campus has perhaps stronger inducements for formal study of cultural subjects, but opportunities for self-education in humanities, social studies, and natural sciences also abound in large cities. Curricular revisions, if they are to encourage advanced education in sciences or humanities, must provide for courses to be taken without regard to credit either for advanced degrees or for the medical degree. To stifle curiosity and discourage spontaneity is to impose on a faculty the burden of bored pupils. To reduce the required core of medical instruction to a minimum and to provide real freedom of choice in the studies of the physician is perhaps the most urgent need in medical education today.

It is obvious that university trustees and administrators, always under great financial pressure to meet current expenses, do not give up a going concern which it would cost millions of dollars to replace unless they feel some great need for change.

From the Department of Medicine, State University of New York, Downstate Medical Center.

In this case, concern over the cultural education of medical students was decisive. Many fine medical schools are miles from the university campus—Johns Hopkins, Harvard, University of California at San Francisco, University of Southern California, Tulane, and Washington University. A few are scores or hundreds of miles from the university—Cornell, Illinois, and Kansas. The issue raised by Johns Hopkins and Stanford, and going back at least to Chaucer's day, is clearly one of great importance, especially if it can be met only by moving the medical schools.

Because of the increasing population and increasing per capita demand for medical care, it is obvious that facilities for medical education in the United States will have to be greatly increased. Costs will be the main restraining factor, with lack of personnel next. It therefore is necessary to seek answers to the questions of where it is best to have the medical student receive his education and of how personnel can best be used to provide education for all professions.

The reason that medical schools are not on university campuses is obvious. Only state-supported schools can afford to operate hospitals, and the largest concentrations of patients exist in large cities, where funds, municipal or charitable, support the great hospitals used for teaching. At Harvard and at Washington University in St. Louis the medical schools were built to be near indigent patients and busy clinicians rather than the university. Prosperous donors, who want the best medical care, usually live or make their fortunes in large cities and support the great private teaching hospitals. But even in some state schools, such as the University of California at San Francisco, consideration of the able clinicians, who are concentrated in the city and not the university towns, may establish the advisability of having medical students away from the campus and in a lively metropolis noted for its cultural activity.

In the past, American university towns provided little culture; one had to go to cities for music, museums of art, theaters, and examples of great architecture. Today, with tapes and records, one can study great music in submarines under one pole or snow-bound camps on the other, as well as in remote ranches or villages. Television and the cinema bring great acting, as well as trash, to most college towns.

Literature could always be studied away from libraries, and the rail-splitter in his cabin in Illinois learned more about English prose and humanity from the Bible and Blackstone than his fellow speaker at Gettysburg from the best schools and colleges of New England. Today there is little advantage in having a medical school in a city in order to provide the students with a cultural environment. With the increase in the number of paying patients and their participation in medical education, and the growth of population and number of able clinicians in university towns, the need for placing medical schools near city hospitals or heavily endowed charity hospitals, with large private patient facilities to attract good clinicians, is gradually becoming less urgent. Thus the reason for building a medical school far from the college town is rapidly vanishing at a time when the opportunity for self-education in the arts and humanities, anywhere on earth, is greatly expanded.

Another reason for having the medical school away from urban congestion has become obvious in the last two decades. More and more prosperous young married people live in suburbs, and the husbands, including a high proportion of full-time medical school faculty members in metropolitan areas, waste two or more hours of each day commuting. Putting the medical school on a suburban campus or in a college town ends this. The temptation to work a five-day week, to which not a few faculty members have succumbed, is removed. When the university is in a great city, as are Columbia, Pennsylvania, and Chicago, the best hope is for developing a pleasant "college village," with adequate open space and grammar schools, near the campus. Perhaps, in future evaluation of colleges, the percentage of full-time faculty members living within two miles of the school will be considered. Certainly the move at Stanford has enabled faculty members to move closer to the college of medicine.

If we agree with Dobzhansky that man is unique in having a "genetic basis for the capability for extragenic transmission of a body of learned tradition called culture," we will agree that failure to receive an optimal amount of culture is a personal misfortune, comparable to deafness or blindness. It is also a misfortune for the community, for failure to transmit to a maximal number of citizens the largest and best parts of our tradition is the surest way to worsen human condition and return to primitive ways. The transmission of culture to physicians and to all other citizens is therefore the most important and truly human function of society, and the nation should prepare to meet whatever changes are needed to aid this process.

It would, of course, be most interesting to give spot examinations on the cultural level of recent medical graduates of Cornell, Harvard, Johns Hopkins, and California at San Francisco, which are not near the university campus, and to compare the results with those of similar tests for graduates of the universities of Minnesota, Michigan, Chicago, and California at Los Angeles, who have been in schools on the campus. My impression that there is no difference either between the most cultured or between the least cultured graduates of these two groups of schools may prove to be erroneous, and a real advantage of one kind of school over another might be established. It should be emphasized that culture is largely transmitted by books, and the knowledge of literature, history, and biography, rather than appreciation of music, fine arts, or the stage must be regarded as the basis of culture. Yet the examination of the young physician's culture should cover a wide spectrum. In a few years, comparisons can be made between the future graduates of Stanford and Johns Hopkins and the graduates of those schools which continue to offer only medical courses to students admitted to medical school. The end of the year of internship would be the best time for such tests, and, for good measure, the same tests should be given to a cross-section of the preclinical and the part-time and full-time clinical teachers as well as to administrators and trustees of the medical college. The tests would be taken anonymously and results reported only according to categories and age groups. The cost of examining the cultural status of physicians would be a small fraction of the amount that foundations have contributed for study of the medical curriculum and minute compared to the cost of moving one school from an urban site to a suburban campus in order to raise the students to a higher level of culture.

Interest in Culture

Those who draw plans for new medical schools or consider making changes in the existing ones will give careful consideration to the experiments at Stanford and Johns Hopkins. In any attempt to raise the cultural level of physicians in the United States, one must contend with the lack of respect, if not contempt, with which the great literary and artistic traditions of humanity are treated in North America. In New York City, musical comedies of little merit draw crowds for years, while a moving production of Tolstoi's "Power of Darkness" will draw an audience of about 200 on good nights for a few weeks. Cultured physicians, like cultured governors, are considered a bit odd rather than exemplary. In plans for a more intense cultural education for physicians this opinion must be taken into account, for many fledgling physicians share the national attitude and are repelled rather than attracted by obligatory courses in humanities or social sciences.

In the English language we have many forceful statements of the problem which disturbs all teachers: "You can lead a horse to water but you can't make him drink." Francis Bacon observed that "the best part of a man's education is that which he gets for himself." Gibbon, ruminating on the folly and lack of cultural interests of so many well-educated Roman emperors, concluded that "the power of education seldom has any efficacy save in those happy dispositions where it is almost unnecessary." The new testament (Luke 16:19-31) gives an astounding picture to illustrate this widely recognized problem. The young teacher told his disciples how father Abraham in heaven had replied to Lazarus' plea from hell that the transfigured beggar be allowed to return to earth and warn his relatives of the truth about the hereafter. Said Abraham: "They have Moses and the prophets; if they hear them not, neither will they be persuaded if one rise from the dead." Christ knew that the death and resurrection of a Messiah would not influence men to adopt the golden rule or follow the Ten Commandments if they had ignored the teachings of their parents and the writings available to all men.

The general resistance to cultural influences, noted by keen observers for two millenniums, and the antagonism to culture peculiar to the United States may make some feel that it is hopeless to expect young persons to benefit from an opportunity to take additional college courses during the years they spend in schools of engineering, law, business, or medicine. These doubters will feel that those persons whose curiosity about the humanities and social sciences has not been awakened by school, family, friends, or newspaper and magazine articles, by the time they are 18 years of age, are not going to have any real interest in such topics while seeking to get ahead in professional courses. The doubters will recall that many highly cultured physicians have had no college courses at all. Sir James MacKenzie, the widely read and profoundly humane physician who revolutionized our view of heart disease, spent 90 hours a week as a druggist's apprentice during the time he was 15 to 21 years of age; he entered Edinburgh medical school with little more than grammar school education. Laennec, the greatest clinician of the 18th and 19th centuries, conducted ward rounds in Latin but had no cultural courses after the age of 17 years. He had taken courses in natural science, Latin, and Greek for two years after he started his work in the hospital as a medical student, before his 15th birthday. He was also a passionate flutist and lover of music.

On the other hand, many business and professional men with A.B. degrees from fine colleges exhibit a complete lack of cultural interest in later life, an atrophy of the mind not unlike the softening of the body of those athletes who become completely sedentary after college. Obviously all these facts were known to the authorities at Stanford and Johns Hopkins, but they must have concluded that none of the facts negated the thesis that "a fine education enhances a native talent" or justified a hopeless attitude toward improvements in teaching. Christ, Francis Bacon, and Gibbon devoted themselves to instructing those who would learn, and it is this group for whom the curricular changes were instituted.

The current system of selecting students for medical school rarely places much value on the curiosity and zeal for self-education which, along with having cultured parents and spending one's childhood and adolescence in a cultured neighborhood, form the real basis for an interest in the great traditions and in the cultural growth of the race. Overcrowded schedules and busy professional lives make it certain that only those students who have curiosity and whose interests have been directed into cultural fields before they go to college will show any real cultural improvement during the late teens and 20's. After they have reached the age of 30 years, especially if they happen to have cultured wives and friends, business or professional men may show a genuine devotion to learning which will continue through life and predispose their children to seek culture. But this phenomenon is often most striking in those who are curious but had little formal drill in the humanities before they entered a professional school. Herbert Hoover is an outstanding example of a person with this broadening of interests. He has always read widely and wisely, and when he was in his 40's he helped translate and publish Vitruvius' textbook on mines and mining in the Middle Ages. Those whose social status and satisfaction in their education have been provided by a college degree are more apt, when they are middle-aged, to take up horticulture, gourmet cooking, ornithology, or some other hobby to which they were not immunized by formal education taken for a degree rather than to satisfy curiosity.

Curriculum and Environment

Between the ages of 16 and 35 years, people entering professional fields have little time to explore new aspects of culture. The opposite sex and establishment in a profession make all other aspects of life seem remote, but acquisition of culture does continue among those "happily disposed" by nature and nurture. If it is made attractive because they admire cultured teachers and have easy access to books, theaters, concerts, and art museums, they make greater gains, and those not so well disposed are less likely to lose interest in culture if they are in a good environment during this period.

One way in which any medical school can further cultural growth was pointed out to me by Sir George Pickering, Regius Professor of Medicine at Oxford. This is to provide a good classical library in the medical school containing the great books and plays, novels, poetry, works on music and the arts, and books on philosophy, anthropology, sociology, and the history of all the sciences, as well as general history and biography. The use of this library would provide an index of the zeal for culture of the faculty, the interns, residents, and students; it would permit concurrent study of a field somewhat wider than the humanities and social sciences. The cost of such a wing in the medical library would be negligible in view of its contribution to cultural growth during the formative years of the physician.

It is unlikely that required courses in these fields will attract better students to enter medicine, and they may not significantly raise the cultural level of students whose sole interest is in medicine. Even in schools on university campuses it seems unlikely that elective courses in these fields will be selected, even by those students of medicine who already have a lively curiosity about the humanities and social sciences, in preference to advanced courses in mathematics, physics, chemistry, psychology, or biology. The difficult courses in these fields are usually avoided by premedical students, since low grades in them might jeopardize admission to medical school; yet the need for these disciplines becomes evident to any student of biochemistry, physiology, or psychiatry. Forty years ago I was glad to go to summer school and take physical chemistry from Professor Harkins of Chicago after my freshman year in medicine, but this course was not needed for credit and I was not concerned about the grade because it could not affect my class standing. (A reformed versifier, I also took a course on Tennyson and Browning that summer.)

The value of any curricular revision made to encourage advanced education in science or the humanities will be greatest if such courses can be taken with no regard to credit, either for advanced degrees or for the medical degree. Then the teachers will have to deal only with students interested in the courses, and course selection will not be influenced by the reputed ease of getting good grades. Everyone is aware of the demoralization of American students by the required-hours system and the availability of "pipe" courses. Equally glaring is the corruption of the research field resulting from paying undergraduates for doing summer research and giving credit for research fellowships in setting standards for specialty certification. When Opie and MacCallum did undergraduate research on malaria, or Grant and Mudd on the tetany during hyperpnea, or Best on glycosuria, no academic credit was given, and the department head did not wonder whether they had come to satisfy curiosity or to get cash or credit. Today the goal of students is not so clear, and opportunity for research by students with genuine curiosity is lessened because of the time and facilities wasted on credit-seekers.

There is strong evidence that an increase of 20 to 50% in the number of physicians graduated each year is needed to take care of our growing population, and the increase should be even greater if we are to provide schooling for foreign students and physicians planning to work and teach in the less favored younger nations. Yet every dean and admissions committee member feels that there are not enough qualified people applying for medical training today. To remedy this situation more superior students should be admitted to medical school after two years of college, and the required number of hours in every department should be cut to the minimum accepted by state or national board examiners. This would give intelligent students more time to devote to those phases of medical, humanistic, or scientific study which really interest them. Teachers in the required courses can do much to make clear the value of making up defects in basic education or broadening one's interest in culture and the living world. If time is made available without increasing the number of years spent in medical school, many students would take advantage of opportunities to study in libraries, night schools, or summer schools and, in medical schools which are part of the university community, in the college or graduate schools.

Sound and inspiring teaching in the preclinical sciences leaves no doubt in a student's mind that mathematics, organic chemistry, and physical chemistry would be invaluable training for which the curriculum made no provision whatever. Similarly, the teaching of Osler, Cushing, Herrick, and other cultured physicians has awakened a desire for better acquaintance with literature and history in many medical students and interns, and probably the teaching of outstanding men in psychiatry and environmental medicine has created in some students a desire to do advanced study of psychology and the social sciences. Only the most gifted and eager student is likely to profit by advanced study in all three fields simultaneously, but opportunities and facilities for such study in one or more fields seem desirable for medical students. When the medical school is on the campus, perhaps instructors and professors will also take courses in mathematics, science, and humanities and set an example to their classes.

The curriculum suggested would allow the average student to take as many hours in medical school courses as are necessary to prepare him for the type of practice he plans to enter, while giving time for additional medical studies for slow learners and for nonmedical studies by those with such interests. This program, and correlation of courses in the medical school with courses in the college or postgraduate schools in other fields, can be put into effect now by the many schools already on university campuses. Elsewhere, various arrangements could be made, depending on the community in which the school is situated and the distance from a large or at least well-rounded library, to encourage students to study and to discuss with a faculty member cultural or scientific fields in which they have a mutual interest.

Thus, on the sound pedagogical principle that leading horses to water is futile when they are not thirsty, one may provide as much good water as possible, knowing that thirsty horses will seek it out. In this way the facilities for additional education and time for additional study in the fields most profitable to each student can be offered to every medical student. Some may prefer to improve their golf or skill at cards if the faculty can interest them only in the courses required to meet licensure qualification. It is better for students to use their spare time playing games than it is to impose on instructors and professors the burden of bored pupils. Zealots for culture may need to be reminded that Hopkins' great dean, Professor William Welch, devoted many hours each week to whist during his academic years, preferred baseball to Brahms, and burlesque to Chekov.

Providing free time and then insisting that it be filled with required "electives" is not going to develop power of discrimination, nor will such a program produce dedicated students or cultured physicians. On the other hand, making available a wide range of self-educational programs and opportunities for advanced study and research and offering no academic reward for time well-spent or penalty for time wasted serves to develop judgment and responsibility in young people and makes it easy for an intelligent faculty to distinguish the sheep from the goats in their flock. It is absurd to say that it is unwise to entrust the disposition of free time to young men and women when we know that in two or three years they will be responsible for decisions on which life or livelihood for many patients will depend. The sense of responsibility for the lives of others can best be developed by having responsibility for choosing what to do with one's own life, or that small fraction of the day not occupied by essential duties. "I cannot praise a fugitive and cloistered virtue, unexercised and unbreathed, that never sallies forth to look upon her adversary, but slinks out of the race where that immortal garland is to be run for, not without dust and heat." Neither Milton's imagery nor Harvey's profound biological insight would have reached heights which astonished the world if their early years had been occupied by a rigid curriculum and required hours in "elective" courses rather than in the freedom of study granted even to youths 17 years of age at Cambridge.

Summary

To reduce the required core of medical instruction to a minimum and to provide real freedom of choice in the studies of the physician is perhaps the most urgent need in medical education today. In the medical schools already on the university campus it is possible to offer a wide choice of studies. When this is not the case, it may be worthwhile for medical school faculty members to assist the cultural and scientific growth of students, an experience entirely missing when the college automatically provides instruction in all these fields. Variety in types of medical schools, as well as in the educational experience of medical students, is far more important than a uniform "ideal" curriculum or a uniform "ideal" medical educational center. Few medical schools can scrap the existing plant and start anew, but all can increase the use of the facilities they have; provide better library facilities for self-education in humanities, social, and natural sciences; and carry out experiments in improving the selection, admission, and education of their students. In planning the necessary new schools, advantages of urban location or campus sites will have to be considered from many angles, since both have many valuable features.

450 Clarkson Ave. (3).

EIGHTH NATIONAL INTERN MATCHING PROGRAM

Ward Darley, M.D., Fred Meier
and
Alice Skarzynski, Evanston, Ill.

In 1959 about 96% of the 6,850 students graduating from United States medical schools and 98.1% of 834 hospitals having approved internship programs participated in the National Intern Matching Program. The hospitals accepted 6,478 interns in this manner, and 251 students failed to secure internships through the services of the program. In 89% of the matches made, both the hospital and the students were able to obtain their first or second respective choices.

This will be the eighth annual report of the National Intern Matching Program (NIMP). Some, but not all, of the basic data that have characterized previous reports are being continued. Some data that have not been published for several years are being brought up to date and other data are being included for the first time. The data that may be missed are those which have shown the distribution of matched internships according to nature of hospital affiliation, amount of stipend, and number of interns sought and matched. A review of last year's report, tables 5 through 16,[1] will reveal that these data were handled in such a way as to show the changes that had occurred between 1953 and 1958. It is now planned to repeat the presentation of these tables only as further changes may justify—perhaps once every two or three years.

In table 1 are reviewed the numbers and percentages of United States graduates and approved hospitals and internship programs participating in NIMP since its first report in 1952. While the initial participations were all over 90%, it was not until 1955 that the present high levels were reached. The percentage of participation of United States graduates is lower than that for hospitals and programs, for a variety of reasons. A few students deliberately stay out of the program, some to take an internship in a hospital awaiting approval and one, therefore, that is not yet eligible for participation. A small number do not take an internship or defer internship because they go directly into research or graduate study. The principal reason for nonparticipation is a decision to intern in a nonparticipating hospital. This situation applies particularly to Tennessee; the University of Tennessee graduates about three-quarters of its seniors at times of the year that do not fit into the NIMP timetable. Thus those hospitals, most of them in Tennessee, that wish to accept students who graduate at odd times, find it necessary not to participate.

Table 2 continues the tabulation of general data that has characterized previous reports. As predicted in last year's report,[1] because of the decision of NIMP to require screening by the Educational Council for Foreign Medical Graduates, there was a sharp drop in foreign graduate participants (376 to 4). Because of this, a considerable drop in the number of graduates going unmatched also was predicted. Table 2 shows that this proved to be the case. Beginning with the 1960-1961 program, the number of foreign participants will again increase and, as a consequence, because of ECFMG screening, it is predicted that the percentage of foreign graduates matched will show a substantial increase over previous years.

Tables 3 and 4 show the type, number, and percentage of internships offered and filled through NIMP for 1952, 1954, and 1959. The number of rotating general internships offered has increased, but the number and percentage matched has dropped. The number of straight internships offered and the number matched have increased and as a consequence the percentage matched has shown a sharp increase—59 to 75%. The category "other internships" includes miscellaneous types of mixed internships with varying kinds of emphasis; consequently, they cannot be classified as either rotating or straight and must be dealt with separately. These kinds of programs and internships are falling off in number but have shown a slight gain as far as their percentage of matches is concerned.

The recent drop in the percentage matched for all internships is a reflection of the fact that the number of internships being offered is growing proportionately faster than the number of available graduates. Of the straight internships, except for those in obstetrics and gynecology, there has been a slight increase in number and also an increase in the percentage matched. For each of the three years noted in table 3, the total number of straight internships offered as a proportion of all internships offered has retained approximately the same relative position—10.5, 9.5, and 11.4%, respectively; but of the total number of all internships matched, the share falling to the straight internship has shown a modest increase—11.7, 12.0 and 16.3% respectively. (Both of these calculations are made from but not shown in table 3.)

Tables 5, 6, and 7 show the continued leveling off of the number of internship applications per student, the percentage of students matched by order of choice, and the hospitals' ranking of students with whom they were matched. In past reports it has been assumed that the downward trend (1952 to 1958 particularly) in the percentage of students being matched for first choice was an indication that students were adding, as first choice, institutions in which they felt their chances for acceptance were open to question but in which they would like to intern if they possibly could. Students can feel free to make such "tries," because in such instances they are not hurting their chances for their second and third choice hospitals—hospitals which otherwise they would list in first and second places.

Table 8 reports a more definite analysis of what happens as between students who make few choices and those who make many. Students who make fewer applications tend to be matched with hospitals that fall the shortest of filling their quotas. As the number of applications increase, the chance of being matched with a hospital that fills or comes close to filling its quota is increased.

While last year's report [1] dealt in detail with the background, history, mechanics, and timetable of the NIMP, it did not indicate the manner in which compliance with the program's agreements was administered. After eight years' experience, a discussion of this aspect of the matching program is indicated.

Table 1.—*Number and Percentage Participation of United States Graduates and Approved Hospitals and Programs, 1952-1959*

	1952	1953	1954	1955	1956	1957	1958	1959
Total United States graduates participating	5,617	5,947	6,258	6,533	6,430	6,498	6,576	6,562
Total United States graduates	6,153	6,418	6,672	6,870	6,719	6,689	6,862	6,850
Percentages of U. S. graduates participating in NIMP	91.3	92.7	93.8	95.1	95.7	97.1	95.8	95.8
Hospitals participating in NIMP	795	808	820	814	821	822	819	818
Total approved hospitals	826	833	836	826	834	833	835	834
Percentage of hospitals participating in NIMP	96.2	97	98.1	98.5	98.4	98.7	98.1	98.1
Total intern programs offered	1,068	1,102	1,032	1,056	1,063	1,052	1,062	1,069
Total approved intern programs	1,102	1,130	1,048	1,068	1,076	1,063	1,078	1,085
Percentage of programs participating in NIMP	96.9	97.5	98.5	98.9	98.8	99.0	98.5	98.5

In the first place, it must be remembered that, for both hospitals and graduates, the decision to join the program is voluntary. A hospital or student, once this decision has been made, applies for, signs, and returns the appropriate agreement. The board of directors of NIMP, which consists of three representatives each from the American Medical Association and the Association of American Medical Colleges, two from the American Hospital Association, one each from the Catholic and Protestant Hospital Associations, one from the Student American Medical Association, and another student representing the national medical student body at large, establishes the terms of these agreements, must authorize any changes therein, must decide questions relative to their interpretation, and, finally, must approve any action taken in connection with their infraction. The hospital and student agreements for the 1960-1961 program follow.

Table 2.—*General Results, 1952-1959*

Year	Hospitals Participating	Intern Programs Offered	Total Positions Offered	Total Positions Filled No.	Total Positions Filled %	Number Unfilled Positions	Students Participating	Students Unmatched
1952	795	1,068	10,414	5,564	53	4,850	5,681	117
1953	808	1,102	10,971	5,744	52	5,227	6,033	289
1954	820	1,032	10,729	6,051	56	4,678	6,412	361
1955	814	1,056	11,075	6,379	58	4,696	6,713	234
1956	821	1,063	11,459	6,588	57	4,871	6,821	233
1957	822	1,052	11,804	6,539	55	5,265	6,923	384
1958	819	1,062	11,958	6,734	56*	5,224	7,131†	397
1959	818	1,069	12,250	6,478	53	5,772	6,729	251

* Incorrectly carried in the Seventh Annual Report as 52%.
† Incorrectly carried in the Seventh Annual Report as 7,031.

Hospital Agreement

On behalf of the hospital named above, I agree to abide by the regulations of the National Intern Matching Program for appointment of interns for first-year internships for 1960-1961 (starting service from April 1 through Dec. 31, 1960).

In particular, it is understood that this hospital is agreeing to (1) offer internship appointment to all applicants matched with this hospital by the matching program, the matched students being the highest ranked students on this hospital's confidential ranking form who wish to intern here more than at any other hospital available to them; (2) restrict internship appointment for United States and Canadian applicants to participants designated for this hospital through the matching program, until after notification of the selections made through the matching program; (3) make or require no commitments or contracts with United States or Canadian applicants prior to the notification of the selections made through the matching program; (4) abide by the official schedule, including accepting no applications from participants in the matching plan after Jan. 25, 1960, and rating applicants and returning rating form by Jan. 30, 1960, offering formal appointment promptly to persons matched by the plan with this hospital no later than March 31, 1960; (5) not accept an intern who was matched elsewhere and subsequently not released (this condition was made a part of the agreement beginning with the eighth matching program); and (6) pay a service fee of $4 for each intern matched through the plan.

We understand further that, although we may freely discuss any matter we choose with the student, no participating hospital has the right, under the plan, to demand or to require that the student state how he will rank this hospital on his confidential rating blank. We also understand that the student has no right to request or to demand that this hospital inform how it plans to rate him.

Furthermore, any statement or other expression concerning how this hospital intends to rank an applicant or how that applicant intends to rank this hospital, which may be made during the free discussion between the hospital and the student, is subject to change based on further considerations. We understand that we, as well as the student, have the right to change our minds at any time prior to the submission of the official confidential rating blanks.

TABLE 3.—*Types and Number of Internships Offered and Filled Through NIMP Since 1952*

	Rotating General Internships			Straight Internships			Other Internships			All Internships		
	1952	1954	1959	1952	1954	1959	1952	1954	1959	1952	1954	1959
Program no.	1	3	8	1	3	8	1	3	8	1	3	8
Number offered	8,596	9,343	10,453	1,098	1,025	1,398	720	361	399	10,414	10,729	12,250
Number matched	4,479	5,092	5,141	656	728	1,060	429	231	277	5,564	6,051	6,478
Percentage matched	52.1	54.5	49.2	59.7	71	75.8	59.6	64	69.4	53.4	56.4	52.9

The confidential rating blank submitted by this hospital and confirmed, is to be the sole determinant of the order of our preference among our applicants.

Student Agreement

I agree to participate in and abide by the results of the matching plan for internship appointment. In particular, I understand that I am agreeing (1) to apply for internship appointment only to hospitals and the federal services registered in the matching plan until after the matching plan results are announced. I understand that an official directory listing the cooperating hospitals and federal services will be available in October, 1959; (2) to accept appointment to the hospital or federal service with which I am officially matched, that hospital being the highest one on my preference list having a place available for me. I understand that I cannot avoid accepting an internship to which I have been matched without a written release from the hospital concerned—also that another hospital that is a member of NIMP cannot accept me as an intern unless I have this release (this sentence was made a part of the agreement beginning with the eighth matching program); (3) to abide by the official schedule, including ranking the internships for which I have applied and returning my confidential ranking form before Feb. 1, 1960; and (4) to send herewith a nonrefundable fee of $2 to help cover the costs of participation in the matching plan.

TABLE 4.—*Type and Number of Straight Internships Offered and Filled Through NIMP Since 1952*

	Medicine			Surgery			Pediatrics			Obstetrics-Gynecology			Pathology		
	1952	1954	1959	1952	1954	1959	1952	1954	1959	1952	1954	1959	1952	1954	1959
Program no.	1	3	8	1	3	8	1	3	8	1	3	8	1	3	8
Number offered	503	546	674	364	358	425	121	113	209	51	8	27	59	...	63
Number matched	359	434	586	202	231	310	69	62	121	11	1	5	15	...	38
Percentage matched	71.4	79.5	86.9	55.5	64.5	72.9	57	54.9	57.9	21.6	12.5	18.5	25.4	...	60.3

It is my understanding that I am free, under the matching plan, to make personal contacts with any participating hospital in which I am interested and to apply to as many of these hospitals as I wish and to rank them according to my judgment.

I understand further that although I may freely discuss any matter I choose with the hospital, no participating hospital has the right, under the matching plan, to demand or to require that I state how I shall rank that hospital on my confidential rating blank. I understand also that I have no right to request or to demand that that hospital inform me how it plans to rate me.

Furthermore, any statement or other expression concerning how I intend to rank a hospital or how that hospital intends to rank me, which may be made during the free discussion between the hospital and myself, is subject to change based on further considerations. I understand that both the hospital and I have the right to change our minds at any time prior to the submission of the official confidential rating blanks.

My confirmed confidential rating blank, giving my order of preference, is to be the sole determinant of the order of my preference among the internships for which I have applied.

I understand that resignation from the matching program can be made only with the approval of my dean, and that no resignations can be accepted after Nov. 14, 1959.

I agree to conduct myself in conformity with the high ethical standards expected of members of the medical profession.

General Comments

Withdrawal from the program is optional for both hospitals and students, if the timing and manner of withdrawal comply with the timetable and provisions of the signed agreements. In the case of student withdrawal, the concurrence of the respective dean is required. Within two weeks after the matching results have been announced, students and hospitals should recognize their matchings by formal contract. The NIMP agreements with both student and hospital can be considered satisfied as soon as the intern begins service. These procedures tie in with the following statement, which appears in "Essentials of an Approved Internship" of the Council on Medical Education and Hospitals of the American Medical Association.

TABLE 5.—*Applications per Student*

Year	Students, No.	Applications, No.	Applications per Student, No.
1952	5,681	21,728	3.8
1953	6,033	19,416	3.2
1954	6,412	21,579	3.4
1955	6,713	25,617	3.8
1956	6,821	29,474	4.3
1957	6,923	30,434	4.4
1958	7,131*	32,090	4.5†
1959	6,729	29,416	4.4

* Incorrectly carried in Seventh Annual Report as 7,031.
† Incorrectly carried in Seventh Annual Report as 4.6.

> *Hospital-Intern Agreement.*—A formal agreement in which mutual obligations are defined should be entered into between the hospital and the applicant at the time of his appointment. This agreement must be honorably fulfilled by both parties and should be terminated only by mutual consent. A breach of the agreement by either a hospital or an intern is not condoned by the Council. Whenever complaint of such a breach is made, it is the policy of the Council to ask each of the parties involved to submit an explanatory statement. Such statements become a part of the physician's and the hospital's record and are made available on request to authorized agencies.[2]

The few questions of irregularity that do occur, unless resolved early in their development, can become complicated and difficult. Therefore, once a hospital, student, or dean is aware of a question that can lead to possible infraction, experience has shown that the quicker such is made known to the NIMP office, the better. Most such situations are the result of failure to read the NIMP agreements carefully, lack of understanding, or inadequate communication. The NIMP office, communicating with the appropriate deans, students, and hospitals, has usually been able to assist with the resolution of these questions to the satisfaction of all concerned. Of course, reports of irregularity that are not supported by a statement of the pertinent facts and a willingness to be quoted do not lend themselves to investigation.

TABLE 6.—*Percentage of Students Matched by Order of Choice*

	Choice			
Year	First, %	Second, %	Third, %	Fourth or Lower, %
1952	84	10	3	3
1953	85	10	3	2
1954	82	11	4	3
1955	76	14	5	5
1956	74	15	6	5
1957	76	13	6	5
1958	74	14	6	6
1959	77	12	5	6

Any cases that go to the point of probable infraction are reviewed by the executive committee of the board of directors and later by the board itself. In case of established infraction on the part of a hospital, the board can determine that copies of the pertinent correspondence be filed with the Council on Medical Education and Hospitals of the A. M. A. If the infraction involves a student, the board can determine that copies of the pertinent correspondence be filed with the Biographical Records Section of the A. M. A. The most common questions of infraction center around the acceptance of a student, without release, by a hospital other than the one to which he or she has been matched. Such instances involve the accepting hospitals as well as the students. As a consequence, when the correspondence pertinent to a proved case of such infraction is filed with the A. M. A., the names of both the hospital and the student will appear.

TABLE 7.—*Hospitals' Ranking of Students with Whom They Were Matched*

Year	Percentage Matched from Rank Group 1*	Percentage Matched from Rank Group 2	Percentage Matched from Rank Group 3	Percentage of Others	Total, %
1956	61	24	11	4	100
1957	71	19	7	3	100
1958	67	22	8	3	100
1959	69	21	8	2	100

* If hospital quota is 10, first 10 men on list form rank group 1 and numbers 11-20 rank group 2, and the ranking continues by groups of 10.

Fortunately, instances of the need for any such action have been rare. In fact, considering the thousands of persons who are involved in the entire NIMP enterprise—hospital administrators and staffs, students, deans, and faculty advisors—the incidence of any kind of difficulty is small indeed. Cooperation on all sides has been the rule. This shows that the principal force that is responsible for the smooth operation of NIMP is the spirit of fair play that originally made the program possible and that has since prevailed.

TABLE 8.—*Comparison of Number of Applications made with Percentage of Positions Filled in Hospitals Where Applicants Were Matched*

Applications Made, No.	1	2	3	4	5	6	7	8	9 and More
Graduates Making Corresponding Number of Applications, No.	885	875	1,219	1,075	766	526	301	245	584
Intern Positions Filled Where Applicants Were Matched, %*	73	73	72	75	77	79	82	83	84

* The percentages of intern positions filled in the hospitals involved were computed by dividing the total intern positions filled by the number of positions offered.

2530 Ridge Ave. (Dr. Darley).

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IMMUNIZATION IN VIRAL HEPATITIS

Joseph Stokes Jr., M.D., Philadelphia

It is paradoxical that zinc-precipitated gamma globulin administered in small doses apparently could protect the recipient against epidemic hepatitis while the same material may produce serum hepatitis. Cold-ethanol-fractionated gamma globulin does not produce serum hepatitis but protects almost all exposed susceptible persons against the more severe symptoms of epidemic hepatitis. The most likely explanation is that in the carrier state hepatitis viruses of more than one antigenic strain are present in the blood stream and that the recipient of the carrier's blood can be protected by gamma globulin in accordance with how closely the transfused virus strain is antigenically related to the strain or strains responsible for epidemic hepatitis. The so-called passive-active immunization afforded by gamma globulin in epidemic hepatitis seems promising, and a method of testing it in closed institutions is proposed.

In the latter part of 1944, during World War II, gamma globulin of the American National Red Cross pools of plasma, fractionated by the cold-ethanol method of Cohn and Oncley, provided effective protection against infectious or epidemic hepatitis with jaundice, both in the armed services and in civilian outbreaks.[1] From the earliest studies on the epidemic disease it became increasingly clear that gamma globulin did not prevent infection with the virus but only reduced symptoms such as jaundice and that even in those exposed susceptible persons who had been injected with gamma globulin and later had no symptoms and negative results of liver function tests, infection probably still occurred. Thus developed the concept of passive-active immunization, as suggested by four widely separated outbreaks and injection of varying doses, ranging from 0.005 to 0.06 ml. per pound of body weight.[2]

Perplexingly, it remains a fact that such a blood product, obtained from the pooled blood plasma of adults, about 2 to 3% of whom are carriers of hepatitis virus in their blood, nevertheless has been universally protective against jaundice in literally hundreds of outbreaks of the epidemic disease. The figure of 2 to 3% of adult carriers is drawn from the fact that about 1% of persons transfused with single transfusions of whole blood in the United States and other nations contract hepatitis with jaundice. Since there will be at least one case, and possibly two, of hepatitis without jaundice for every case of hepatitis with jaundice which resulted from infective material, it is apparent that at least 2 to 3% of adult populations must be considered carriers. Unfortunately, no adequate tests for detection of this 2 to 3% of carriers are available.

To explain the puzzle of the protection provided by gamma globulin against parasites with which it has been intimately associated in the pools of plasma before ethanol fractionation, several hypotheses deserve consideration.

Possible Reasons

First, the most probable explanation is that the carrier state often occurs with hepatitis virus strains that are antigenically different from the epidemic strain or from strains of virus against which gamma globulin in small doses is so effective.

Second, in the carrier state the neutralizing antibody may be combined with the antigen and may be slowly dissociated from the latter during the long incubation period in the recipient, after the whole blood has been injected. Thus a latency of the antigen-antibody complex in the donor may be disturbed by the nonresistant recipient, who lacks the capacity to hold the virus in a latent or neutralized phase. If such separation of the virus-antibody complex occurs in the recipient, the virus may then infect, unless unusually large doses of gamma globulin are given immediately after transfusion and again one month later, when the dissociation has occurred and the long incubation period is well under way.[3] This possible explanation is apparently more attractive to those who feel that hepatitis viruses are all antigenically similar.

Third, a few cellular elements may be present in the pooled plasma that is used for fractionation, and the virus may be present in such cells, or fractions of cells, and thus may not be readily attacked by antibody, even though the pooled plasma may have a high titer of neutralizing antibodies to the virus. It is of interest, in this connection, that gamma globulin obtained through fractionation of pooled plasma by the zinc-precipitation method can contain hepatitis virus and in the studies of such fractionation was infective, usually with a long incubation period. Thus we have the paradox of a gamma globulin which can prevent the epidemic disease with jaundice but which has produced serum hepatitis with jaundice when injected parenterally, as

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From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and the Children's Hospital of Philadelphia.

Read in the Symposium on Hepatic Diseases before the Joint Meeting of the Section on Experimental Medicine and Therapeutics, the Section on Gastroenterology and Proctology, the Section on General Practice, the Section on Internal Medicine, the Section on Pathology and Physiology, and the Section on Radiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

demonstrated by Murray in volunteers. (This statement on prevention is not based on clinical trials but on the similar capacity of the zinc-precipitation and ethanol-fractionation methods to concentrate antibodies in the gamma globulin fraction.) The cold-ethanol method tends either to segregate the hepatitis virus in fraction 1, perhaps because of the nature of the molecule or of the antigen-antibody complex, or to destroy the virus in fraction 3, a destruction which does not occur with the zinc method. This may be because of the greater severity of handling in the cold-ethanol than in the zinc method. According to this explanation, latency in the carriers would be an intracellular phenomenon in the blood stream—perhaps in the red blood cells, the macrophages, or the leukocytes—and the antibodies of the plasma would not have access to the virus to inactivate it.

Fourth, the antigen-antibody complex which has been proposed as one hypothesis for the carrier state may actually be represented by a virus-inhibitor complex, in which the inhibitor is not a neutralizing antibody but protein molecules or mucoproteins to which the virus becomes attached and which prevent active infection of the host. Thus, the virus may be protected from inactivation in the presence of even large amounts of antibodies in the blood stream of the carrier. Again, these antibodies may be segregated by ethanol fractionation in the gamma globulin, while either the virus-inhibitor complex may be segregated in fraction 1, or the virus and the virus-inhibitor complex may be destroyed by the severe handling entailed in such fractionation. At the time of whole blood transfusion the virus-inhibitor complex in the blood of the carrier, who is the donor, may be slowly broken up in the recipient. The recipient then may either eliminate the virus or return it to a latent phase, which presumably could occur in tissue cells such as those of the liver, or in the blood—both intracellular and extracellular—or in both the blood and other tissues.

Of these four hypotheses the first, namely, that there are antigenically different strains of hepatitis virus, is the most attractive, because it is the simplest and generally corresponds to the experimental findings obtained in volunteers studied during World War II and immediately afterward. That such immunological problems are rarely simple was well illustrated by what appeared to be contradictory findings at that time in the study of serum hepatitis.

Results of Studies

Whereas small amounts of infective serum to which large amounts of gamma globulin were added in a neutralization test could still successfully infect volunteers,[4] field trials in a large hospital for evacuated casualties from all theaters of war nevertheless demonstrated that two 10-ml. doses of gamma globulin, injected one month apart, protected over two-thirds of the injected group against hepatitis with jaundice, as compared with the incidence in an adequate group of controls selected alternately.[3] In two other controlled field trials, in which only one 10-ml. dose of gamma globulin was used, the average incubation period was greatly lengthened, although the incidence of hepatitis with jaundice was not decreased.

Certainly these latter findings suggest that a slow dissociation of virus and neutralizing antibody or inhibitor is taking place in the transfused blood of the donor after it has entered the recipient, that the second dose of gamma globulin may be attacking the virus after its protective coat has been discarded during the earlier incubation phase, and that the first dose of gamma globulin may only add inhibitor or neutralizing antibody at a time when it may well increase the protective coat and lengthen the time before the recipient's immune mechanisms begin to act on the transfused and partially protected parasite. It was this rationale that originally suggested the use of two doses of gamma globulin at a one-month interval. On the other hand, there may be carriers of both serum hepatitis virus B and of epidemic or infectious hepatitis virus A, and the gamma globulin may give protection after transfusions, in accordance with the proportion of those donors who carry virus A or viruses of antigenic composition similar to A.

Recent additional evidence was obtained by Mirick,[5] with dosages and timings similar to those used in our studies. His studies on tuberculous patients who required whole blood transfusions suggested that injections of gamma globulin provided a protection similar to that obtained in our field studies on evacuated battle casualties, with the exception that Mirick's method included only two doses of gamma globulin, as in our original study, and not one single dose, as in our later studies. This partial protection given by two doses appears sufficiently important to make many persons who have seen the results of both studies at widely separated intervals hesitate to receive a transfusion of whole blood without such succeeding injections of at least two doses of gamma globulin. However, the relatively limited supplies of gamma globulin may deter widespread application of these suggestive findings.

It is difficult, however, to explain the findings in volunteers who were injected with infective serum (SH virus), followed by two doses of gamma globulin (10 ml. each) one month apart, in whom no apparent protection resulted.[4] It is conceivable that the virus with, at times, a long incubation period, even up to 194 days, may assume an inactive form, from which it is activated only in an environment suitable to its development, such as that of the recipient. Again, the reason for such lack of protection could be ascribed far more easily to antigenically different strains of virus.

Results of studies carried out on volunteers also suggest that certain strains of serum hepatitis virus (the virus which is always isolated from the blood, apparently never from the stool, and which usually has a long incubation period) do not produce permanent immunity, in that such previously infected volunteers may be reinfected parenterally and may show active symptoms at sufficiently separated intervals to avoid a suggestion of recidivation. On the contrary, the epidemic disease, on both experimental and epidemiologic grounds, tends to produce a more permanent immunity, particularly when it occurs in the younger age groups. However, the epidemic disease, in older persons, may continue as a subacute chronic infection, with a tendency to relapse and to fibrotic changes in the liver. Serum hepatitis, particularly in older persons, also shares the tendency to chronicity, severe relapse, and fibrosis of the liver.

Possible Applications

In view of the more permanent immunity which, before puberty, appears to occur after epidemic hepatitis and which receives some confirmation from the fact that doses of gamma globulin as small as 0.01 ml. per pound of body weight will protect most persons—at least against the overt disease with jaundice—the question naturally arises whether our far from complete knowledge of the disease would still permit some approach to active immunization, in addition to the passive immunization which has been so universally effective against epidemic hepatitis with jaundice.

Four studies[2] carried out in epidemics during and immediately after World War II, suggested that, in the presence of continued exposure to virus, passive immunization permitted inapparent infection and thus prepared the person injected with gamma globulin for active, and probably permanent, immunity. These studies have recently been confirmed by Ward and co-workers[6] in an institution on Long Island, Willowbrook, N. Y., where controlled studies carried out over several years have indicated the development of passive-active immunization in the resident children, who continued to be exposed to the disease in the institution after injection of gamma globulin (0.06 ml. per pound of body weight). In certain studies by Krugman and Ward,[7] filtrates of stool were used which were titrated by oral infection. The virus strain produced extremely mild disease and the incubation period was unusual in that it ordinarily ranged between 35 and 50 days, about midway between the mean incubation periods of recorded outbreaks of viral hepatitis A and of most outbreaks of viral hepatitis B.

This confirmation of the protection obtained against the more severe aspects of viral hepatitis by means of such a passive-active immunization highlights a suggestion made by our group some years ago that, in lieu of any method of growing the hepatitis viruses, passive-active immunization should be approached first in closed institutions, where epidemics so often occur. It is proposed that, in an institution in which the epidemic disease is pending, a single cottage be selected whose inmates, as far as can be determined, have not been fully exposed to epidemic hepatitis. A pool of plasma, obtained from a number of patients presenting mild cases of the disease during the acute stage and preserved with observance of adequate precautions, would serve as the orally administered infecting agent. Serologic tests for syphilis would be carried out on this pool. A suitable portion of the group in the cottage would be given orally the virus in the pooled plasma, and gamma globulin would be injected intramuscularly at about the same time, in a dose of 0.01 to 0.02 ml. per pound of body weight. Subsequent use of the virus of unknown titer in the pool and the amount of gamma globulin to be injected would depend on the results obtained in the original group. Sufficient experience has been accumulated in the four outbreaks already mentioned and in the recent studies at Willowbrook to warrant confidence in the safety and suitability of this method of immunization. Certainly, in groups of children who have not yet attained puberty even the unmodified virus may, in a mild outbreak, be used with little risk, and in the presence of antibodies, such as gamma globulin provides, there appears to be no danger whatever. On the contrary, this method of immunization could mean the saving of thousands of days of well-being lost to persons with both acute and chronic active hepatitis; the prevention of much chronic fibrosis, or cirrhosis, of the liver; and the prevention of many deaths in adults. Although the epidemiologic evidence in most instances favors permanent immunity to the epidemic disease after one sharp attack with jaundice, only experience with such a method of immunization would indicate how permanent it might be after anicteric infection.

Summary

Gamma globulin, produced by cold-ethanol fractionation from pooled human plasma, has been universally successful in protecting most exposed susceptible persons against the more severe symptoms, including jaundice, of epidemic viral hepatitis. The varying doses of this gamma globulin which are used by different researchers, i. e., from 0.01 to 0.06 ml. per pound of body weight, apparently have permitted anicteric infection with hepatitis virus in such exposed susceptible persons, frequently without symptoms. A number of such infections without symptoms, but not all, may be detectable by repeated transaminase or thymol turbidity tests.

Larger and repeated parenteral doses of such gamma globulin may have some protective value against serum hepatitis which results from parenterally administered blood products. Additional experience is required for final determination of its value for such protection. The paradox of possible protection obtained from zinc-precipitated gamma globulin administered in small doses against epidemic hepatitis, in contrast to the production of serum hepatitis by the same material, and the problem of protection against serum hepatitis are reviewed in several hypotheses, none of which is completely adequate in the absence of serologic tests for hepatitis viruses. Cold-ethanol-fractionated gamma globulin does not produce serum hepatitis. A possible approach to immunization against epidemic viral hepatitis in closed institutions, if successful, might be extended to large groups.

1740 Bainbridge St. (47).

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MULTIPLE INJECTIONS OF CRYSTALLINE INSULIN IN TREATMENT OF LABILE DIABETES

Henry L. Wildberger, M.D.
and
Henry T. Ricketts, M.D., Chicago

Fourteen patients with labile diabetes were treated with divided daily doses of crystalline insulin (CI). Prior to the exclusive use of CI the patients had been treated with protamine zinc insulin and crystalline insulin given separately or mixed, isophane (NPH) or lente insulin in single or divided doses, isophane (NPH) or lente plus crystalline insulin, or globin insulin alone, all of which provided unsatisfactory management. The CI was given in four daily injections, one before each meal and a small dose between midnight and 2:00 a. m. Despite the disadvantages of the nightly injections none of the patients insisted on resuming his previous insulin program. Divided daily doses of CI gave improved control of blood and urine sugar levels and diminished frequency and severity of insulin hypoglycemia.

Treatment of diabetes mellitus with divided daily injections of crystalline insulin is not a novel suggestion. For some years after the discovery of insulin this regimen was the only possible one. With the advent of insulins having a more prolonged action, therapy with crystalline insulin alone was largely supplanted. It has, however, found continued use among selected patients with labile diabetes.

Probably less than 5% of the diabetic population have a labile, brittle, or growth-onset type of diabetes. This group, while not large, presents serious problems in management. Treatment with any of the long-acting preparations of insulin commonly results in wide, unpredictable fluctuations of the blood sugar level so that excessive glycosuria and ketosis may alternate with hypoglycemia.

In 1950 Haunz[1] reported the use of multiple doses of unmodified insulin alone in six such cases. Control of the blood sugar level was clearly better than that obtained with other forms of insulin. We have

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From the Department of Medicine, University of Chicago.

used this neglected method in selected patients since 1943 and now wish to report results in 14 patients.

Procedure

Fourteen patients (12 female and 2 male) were chosen primarily because of the difficulties presented in the management of their diabetes. Five patients had a history of ketosis or ketoacidotic coma, two had diabetic peripheral neuropathy, nine had diabetic retinopathy, and three had diabetic nephropathy with fatal termination. Inpatient records covering 14 to 21 days and outpatient records covering several months to 12 years were reviewed.

Hospitalized patients were given a diet that was constant with respect to amounts of carbohydrate, protein, and fat. Capillary blood specimens for glucose[2] were taken two to four times daily, and 24-hour samples of urine were collected for quantitative estimation of glucose.[3] Fractional urine specimens obtained before breakfast and three hours after each meal were tested qualitatively for glucose. Hypoglycemic episodes were recorded and described.

Comparison of Results in Patients Given Crystalline Insulin and Other Insulin Regimes for Labile Diabetes

	Age, Yr.			Dose		Blood Sugar			Urine Sugar		
							Determinations			Determinations	
Case No.*	At Follow-up	At Onset	Sex	Units, No.	Kind†	Mean, Mg. %	No.	% Within Acceptable Range‡	Mean, Mg. %	No.	% Within Acceptable Range§
1	58	52	F	55	NPH(Div.)	192	15	14	22	6	70
				40-50	PZI+CI	222	15	0	15	23	70
					NPH+CI						
					Lente+CI						
				32	CI	145	7	58	4	7	100
2	38	23	F	40	NPH+CI	201	38	15	86	45	0
				26-39	CI	120	16	56	40	15	13
3	21	5	F	30	PZI	302	26	20	26	12	50
				42	CI	280	38	19	11	21	86
4	24	7	M	40	Lente	357	10	10	36	7	15
				37	CI	138	17	70	0	7	100
5	31	28	F	50	Lente+CI (Div.)	185	20	35	20	9	56
				43	CI	145	18	66	0	6	100
6	29	11	F	70	PZI+CI	176	36	47	11	9	88
				50	CI	164	31	45	2	8	100

* Improvement in both blood and urine sugar levels is seen in two outpatients (cases 1 and 2) when treated with crystalline insulin only. All blood samples were taken 2 to 4 hrs. after lunch. Improvement in mean blood and urine sugar levels and an increase in the percentage of values falling within acceptable range are seen in four hospitalized patients (cases 3, 4, 5, and 6) treated first with long-acting insulin and subsequently with divided doses of crystalline insulin. Blood sugar values represent both fasting and postprandial determinations.

† PZI = Protamine zinc insulin; CI = crystalline insulin.

‡ Acceptable true glucose value, 60-150 mg.%.

§ Acceptable value, less than 20 Gm.%.

Outpatients collected 24-hour urine specimens for quantitative glucose analysis[4] one day prior to clinic visits and often, although not invariably, a specimen of venous blood for glucose analysis[5] was drawn two to four hours after the noon meal. Fractional urine tests performed by the patient at home and recorded by him were noted in his record, with a description of any hypoglycemic episodes. In general, physical examinations were done at least once a year and often more frequently.

All patients were first treated with one or, more commonly, several insulin preparations, including protamine zinc insulin and crystalline insulin given either separately or mixed, NPH or lente insulin in single or divided doses, NPH or lente plus crystalline insulin, and globin insulin alone. Two patients received tolbutamide in addition to a long-acting insulin but showed no significant improvement. Finally, treatment was started with divided doses of crystalline insulin given one-half hour before meals and a small dose between midnight and 2 a.m.

Means of both blood and urine glucose levels were determined for the periods during which the patient was given long-acting insulin and crystalline insulin alone. The percentage of blood-sugar values falling within an acceptable range of 60 to 150 mg. per 100 ml. (true glucose) and the percentage of 24-hour urine specimens containing less than 20 Gm. of glucose were calculated for all periods.

Report of Cases

Mean blood and urine sugar levels for two representative outpatients (cases 1 and 2) are presented in the table. The periods of observation were eight and six years respectively. A decline in hyperglycemia and glycosuria, with an increase in the percentage of results falling within the acceptable range, are seen during treatment with crystalline insulin. Case 1 is noteworthy and somewhat unusual in that the patient developed labile diabetes at 52 years of age. The table shows similar improvement in four hospitalized patients who were given crystalline insulin alone.

Figures 1 and 2 illustrate the daily blood and urine sugar values and corresponding insulin doses for patients in cases 3 and 6 respectively. Initially, marked fluctuation in blood and urine sugar levels was observed. A diminution in these crests and troughs, along with a general decline in glycosuria, occurred in patients treated with crystalline insulin alone.

Prior to treatment with crystalline insulin, hypoglycemia of mild to moderately severe degree occurred in all patients, in some as frequently as once or more each day. In three patients hypoglycemia was severe, causing nocturnal convulsive seizures or periods of irrational, aggressive, and abusive behavior. One patient feared hypoglycemia so much that she refused to leave her home lest she come to harm elsewhere.

When treatment was changed to include crystalline insulin only, hypoglycemia was sometimes noted but usually abated with adjustment of dosage. Ten patients described fewer and/or less severe episodes of hypoglycemia.

The average insulin dose was reduced from 49 units before to 42 units during treatment with crystalline insulin. The mean crystalline insulin distribution for all patients was 34% before breakfast, 17% before lunch, 31% before supper, and 18% between midnight and 2 a. m. The average single dose of crystalline insulin was 10 units, and the highest single dose in any patient was 35 units. The small size of each dose undoubtedly contributed to diminished frequency and severity of hypoglycemia. Insulin lipodystrophy present in two patients prior to treatment with crystalline insulin showed no perceptible worsening in spite of the multiple injections.

Of the 14 patients studied, only 4 failed to show improvement in the control of their diabetes. In two of the four data were inconclusive, and in the remaining two there was no improvement. One of the latter patients was emotionally incapable of adhering to a dietary program and ate in an erratic and inconstant fashion, refusing both medical advice and psychiatric counsel.

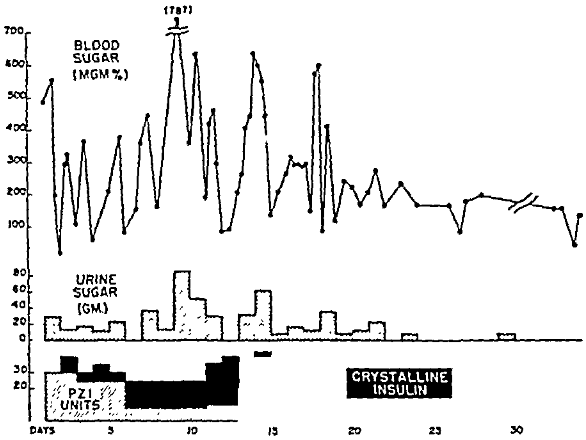

Fig. 1 (case 3).—Graphic record during hospitalization of 21-year-old woman, showing wide oscillations in blood sugar level during treatment with protamine zinc and crystalline insulins. Note diminution in variability of blood sugar level and fall in glycosuria soon after start of treatment with crystalline insulin alone.

Comment

The use of divided daily doses of crystalline insulin has been satisfactory in ameliorating the severity and frequency of hypoglycemia and diminishing fluctuations of the blood and urine sugar contents in patients with very labile diabetes.

The dose of insulin given between midnight and 2:00 a. m. presents the greatest inconvenience to the patient. Some patients have elected to postpone their bedtime until after the midnight injection. Others have retired earlier after filling the insulin syringe and placing it at the bedside with an alarm clock. On being awakened at the proper time they administer their insulin and go back to sleep. Although multiple daily insulin injections are somewhat inconvenient, only one patient in this group expressed a complaint about it, and no patients insisted on resuming their previous insulin program.

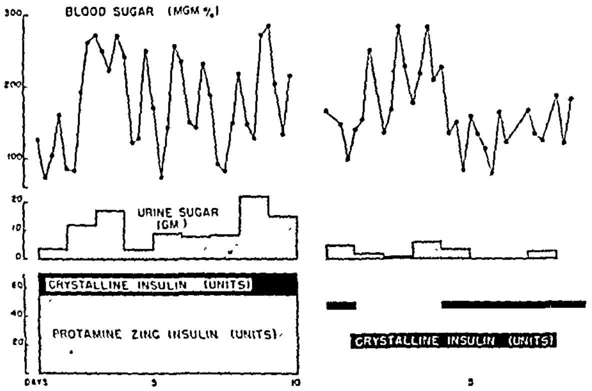

Fig. 2 (case 6).—*Findings similar to those in figure 1 are seen for 29-year-old woman. In addition, total crystalline insulin required is less than total of protamine zinc and crystalline insulin used at first.*

The small size of each individual dose of crystalline insulin provides several advantages to the patient in addition to maintaining better blood and urine sugar levels. Hypoglycemic episodes are easily detected, do not last long, and respond readily to treatment. The 40-unit strength of insulin may be used almost exclusively, affording greater accuracy in measurement than is possible with a more concentrated preparation. It is evident that in some patients the salutary effects of this regimen may not be maximal for several months, and one need not be discouraged by failure to achieve success promptly.

While patients with labile diabetes mellitus are often young or have had an early onset of diabetes mellitus, age does not exclude lability. One of the patients studied was 58 years old and developed diabetes at 52 years of age. Seven patients were over 30 years of age, although the onset of diabetes occurred after that age in only two.

Summary

Of 14 patients selected because of unusual lability of the blood sugar level and failure of long-acting insulins to control symptoms of diabetes satisfactorily, 10 were improved, results in 2 were inconclusive, and 2 were unimproved by the use of multiple injections of crystalline insulin alone.

950 E. 59th St. (37) (Dr. Wildberger).

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TABLES OF AVERAGE WEIGHT AND HEIGHT OF AMERICANS AGED 65 TO 94 YEARS

RELATIONSHIP OF WEIGHT AND HEIGHT TO SURVIVAL

Arthur M. Master, M.D., Richard P. Lasser, M.D.
and
Gloria Beckman, B.A., New York

Provisional standards of height and weight for persons 65 to 94 years of age are here set up on the basis of data from 2,925 men and 2,694 women. All subjects were ambulant, all lived in the community, and all were free from evidence of cardiovascular, renal, or other disease. Weights and heights were measured in stocking feet, and weight included that of light undergarments. For men between the ages of 65 and 69 years the range of stature was from 154 to 185 cm. (61 to 73 in); the average man of this age group was 173 cm. (68 in.) tall and weighed 72 kg. (159 lb.). For women between the same ages the range of stature was from 147 to 175 cm. (58 to 69 in.); the average woman was 160 cm. (63 in.) tall and weighed 64 kg. (141 lb.). In both sexes and at all heights the average weight became lighter with advancing age. Height, unlike weight, virtually did not diminish with further aging. The authors emphasize that the published figures are averages of actual measurements rather than optimal or ideal figures.

This communication will present the results of a survey of height and weight in persons in the healthy population of the United States between 65 and 94 years of age. From these data a table has been developed for this older population, showing average weight in relation to height among men and women in successive five-year age groups. From analysis of the changes in height and weight distribution with advancing age, some inferences have been drawn about the relationship of height and weight to survival after the age of 65 years.

The first table should prove useful as a standard of reference in defining the limits of overweight and in studying the association between height, weight, and disease. It may also serve as a guide for weight control in persons of advanced age.

Weight control has become recognized as an important aspect of preventive medicine. Excess weight, with its attendant increased risk of cardiovascular and renal disease, diabetes mellitus, and gallbladder disease, has already been shown by life insurance investigations to exert an unfavorable effect on longevity in younger age groups. As will be shown, it is a factor of increasing importance after the age of 65 years.[1]

Concern with the problems of geriatric medicine has only recently become widespread because of the pressure of the increasing older population. It has been estimated that 80% of persons who attain the age of 40 years will live to be at least 65 years of age. Furthermore, more than one-half of caucasoid men who celebrate their 65th birthday will survive another 12 years, and one-fifth for 20 years. The outlook is even better for women; one-half of those who reach age 65 will live to the age of 80, and one-fifth will celebrate their 88th birthday.[2] There is every expectation that this degree of

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From the Department of Medicine, Mount Sinai Hospital, and the New York Heart Association.

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survival can be prolonged and health improved by proper attention to such factors as nutrition, physical activity, and mental outlook.

This report represents one facet of a survey of the blood pressure and general health of the older population, conducted by the authors and made possible through the generous cooperation of thousands of physicians throughout the country who furnished these data. The published results of this survey to date have included such observations as that blood pressure rises with increasing weight in both sexes from the age of 65 on but bears little or no relationship to height alone. Blood pressure is related to body build, that is, to the person's weight relative to his height and not to the absolute weight.[3] Women over 65 years of age have consistently higher systolic pressures than men, although their diastolic pressures are practically the same. After 65 years of age blood pressure ceases to rise consistently with age.[4]

Methods

The series on which the study was based was composed almost wholly of caucasoid subjects from all geographical areas of the United States, belonging to all social and economic levels, of various ethnic origins, and engaged in a variety of occupations. All were ambulant, living in the community, and apparently in good health. Persons with histories of cardiovascular or renal disease were excluded.

Height and weight were recorded with subjects in stocking feet and clad only in light undergarments. The weight of these undergarments was not subtracted. The series was divided according to sex and subdivided into five-year age groups. Persons 95 years of age and over were too few in number to be statistically useful.

Table 1.—*Average Weight in Pounds per Inch of Height in Persons Aged 65-94 in Five-Year Age Groups*

	Age, Yr.											
	65-69		70-74		75-79		80-84		85-89		90-94	
Height, In.	M	F	M	F	M	F	M	F	M	F	M	F
58	..	133	..	125	..	123	..	..	..	..	..	..
59	..	134	..	127	..	124	..	116	..	110	..	..
60	..	135	..	129	..	126	..	118	..	113	..	..
61	142	137	139	131	137	128	..	121	..	116	..	..
62	144	139	141	134	139	131	135	124	..	120	..	119
63	146	141	143	137	141	134	136	128	133	124	..	119
64	149	144	146	140	143	137	138	132	135	128	..	120
65	151	147	149	144	145	140	141	136	139	133	130	124
66	154	151	152	147	148	113	144	140	142	138	133	129
67	156	155	155	151	151	146	147	144	145	142	136	..
68	159	159	158	155	154	..	150	..	148	..	140	..
69	163	164	162	160	158	..	154	..	152	..	144	..
70	167	..	165	..	162	..	159	..	156	..	149	..
71	172	..	169	..	166	..	164	..	160	..	154	..
72	177	..	173	..	171	..	170	..	165	..	..	..
73	182	..	178	..	175	..	..	..	..	..	..	..

The average weight at each inch of height was then calculated for each five-year age group according to sex. These crude data showed an orderly but not perfectly consistent progression of weight with increasing height, particularly at the upper and lower extremities of the height range. Therefore, in order to minimize sampling artifacts, the crude data were statistically transformed by use of a "weighted moving average," a statistical technique commonly used for data of this type. The height-weight tables presented here are based on these results. Crude values and the number and distribution of heights and weights in the sample population have been published previously.[5] There were 2,925 men and 2,694 women in the sample.

Table 2.—*Mean Height, Weight, and Body Surface Area in Persons Aged 65-94 Years*

	Age, Yr.											
	65-69		70-74		75-79		80-84		85-89		90-94	
	M	F	M	F	M	F	M	F	M	F	M	F
Mean height, in.	68	63	67	63	67	63	67	62	68	62	67	62
Mean weight, lb.	159	141	155	137	151	134	147	124	148	120	136	119
Mean body surface area, sq.mm.	1.87	1.67	1.81	1.65	1.79	1.63	1.78	1.55	1.80	1.53	1.72	1.53

Another grouping of various height-weight classes was formed by classifying all subjects as either tall, medium, or short and then assigning them to one of four weight groups as follows: underweight—at least 10% lighter than the mean in their height group; average—from 9% lighter to 9% heavier; moderately overweight—more than 10% and less than 25% heavier than the mean; and severely overweight—25% or more heavier than the mean of their respective height group. This classification is the one generally used by insurance companies. Its value lies in that it is possible to follow the effects of aging on height and weight in terms of commonly held mental images of body build. The percentage of subjects falling into each weight and each height group was then determined for successive five-year intervals. Details have been published previously.[3]

Results

Table 1 presents the average weight for each inch of height for persons of each sex in five-year age groups. The height range in men between 65 and 69 years of age is from 61 to 73 in. (154 to 185 cm.); in women of the same ages from 58 to 69 in. (147 to 175 cm.). These ranges are maintained up to the ages of 80 to 84 years, when the smaller size of the total sample compels the omission of the shortest and tallest standards because too few observations can be made. For subjects between the ages of 90 and 94 years, values are statistically credible only for those between 65 and 71 in. (165 to 180 cm.) tall in men and 62 to 66 in. (157 to 168 cm.) tall in women. Women consistently weigh less than men of the same height, except for tall women aged 65 to 69 years.

Weight increases with increasing height as the bony frame becomes larger and heavier. However, the increase in weight for each successive inch of height is not constant but rather increases with increasing height. Thus, in men, weight increases by 2 or 3 lb. (0.9 to 1.4 kg.) per inch of increased height from 61 to approximately 68 in. (155 to 173 cm.), whereas from 68 to 73 in. (173 to 185 cm.) the weight increases by 4 or 5 lb. (1.8 to 2.3 kg.) per inch. In women there is an increase of 2 lb. per inch of height at short to average heights and 3 to 4 lb. per inch at the taller heights.

Changes with age in average weight are striking in both sexes, and a decrease in average weight is noted at each inch of height decrease. For example, the average weight of men 70 in. (178 cm.) tall is 167 lb. (75 kg.) at ages 65 to 69, 165 lb. (74 kg) at 70 to 74 years, 162 lb. (73 kg.) at 75 to 79 years, and 149 lb. (68 kg.) at 90 to 94 years. This decrease of 15 or 20 lb. (7 or 9 kg.) in the average weight of surviving persons over a period of 25 years is seen in persons of both sexes and at each inch level of height. By contrast, mean height changes insignificantly with advancing age, being 68 in. at 65 to 69 years and 67 in. (170 cm.) at 90 to 94 years for men and for women 63 in. at 65 to 69 years and 62 in. at 90 to 94 years (160 and 157 cm.).

Table 2 shows the mean height, weight, and body surface area of persons in each five-year age group. The average man aged 65 to 69 years is 68 in. tall and weighs 159 lb. (72 kg.); aged 90 to 94 years he is 67 in. tall and weighs 136 lb. (61 kg.). The average woman aged 65 to 69 years is 63 in. (160 cm.) tall and weighs 141 lb. (64 kg.); aged 90 to 94 years she is 62 in. tall and her average weight is 119 lb. (54 kg.).

Table 3 presents the range of weight variation encompassed by ±10 and ±20% of the average weight at each inch of height. Traditionally, for younger subjects a permissible range of variation has been considered to be ±20% of the average. However, in this older group, we believe that this may be too broad and that ±10% limits may be more desirable. Thus, for the average man 65 to 69 years of age, height 68 in., the range of desirable weight (±10%) would be 143 to 175 lb. (64 to 79 kg.). For the average woman 65 to 69 years of age, height 63 in., the range (±10%) would be 127 to 155 lb. (58 to 70 kg.).

TABLE 3.—*±10 and ±20% Limits for Standard Weight per Inch of Height*

	Age, Yr.											
	65-69		70-74		75-79		80-84		85-89		90-94	
Height, In.	±10%	±20%	±10%	±20%	±10%	±20%	±10%	±20%	±10%	±20%	±10%	±20%
						Men						
61	156-128	170-114	153-125	167-111	151-123	164-110						
62	158-130	173-115	155-127	169-113	153-125	167-111	148-122	162-108				
63	161-131	175-117	157-129	172-114	155-127	169-113	150-122	163-109	146-120	160-106		
64	164-134	179-119	161-131	175-117	157-129	172-114	152-124	166-110	148-122	162-108		
65	166-136	181-121	164-134	179-119	160-130	174-116	155-127	169-113	153-125	167-111	143-117	156-104
66	169-139	184-123	167-137	182-122	163-133	178-118	158-130	173-115	156-128	170-114	146-120	160-106
67	172-140	187-125	170-140	186-124	166-136	181-120	162-132	176-118	160-130	174-116	150-122	163-109
68	175-143	191-127	174-142	190-126	169-139	184-123	165-135	180-120	163-133	178-118	154-126	168-112
69	179-147	196-130	178-146	194-130	174-142	190-126	169-139	185-123	167-137	182-122	158-130	173-115
70	184-150	200-134	182-148	198-132	178-146	194-130	175-143	191-127	172-140	187-125	164-134	179-119
71	189-155	206-138	186-152	203-135	183-149	199-133	180-148	197-131	176-144	192-128	169-139	185-123
72	195-159	212-142	190-156	208-138	188-154	205-137	187-153	204-136	182-148	198-132		
73	200-161	218-116	196-160	214-142	192-158	210-140						
						Women						
58	146-120	160-106	138-112	150-100	135-111	148- 98						
59	147-121	161-107	140-114	152-102	136-112	149- 99	122-100	133- 89	121- 99	132- 88		
60	148-122	162-108	142-116	155-103	139-113	151-101	130-106	142- 94	124-102	136- 90		
61	151-123	164-110	114-118	157-105	141-102	154-102	133-109	145- 97	128-104	139- 93		
62	153-125	167-111	147-121	161-107	144-118	157-105	136-112	149- 99	132-108	144- 96	131-107	143- 95
63	155-127	169-113	151-123	164-110	147-121	161-107	141-115	154-102	136-112	149- 99	131-107	143- 95
64	158-130	173-115	154-126	168-112	151-123	164-110	145-119	158-106	141-115	154-102	132-108	144- 96
65	162-132	176-118	158-130	173-115	154-126	168-112	150-122	163-109	146-120	160-106	136-112	149- 99
66	166-136	181-121	162-132	176-118	157-128	172-114	154-126	168-112	152-124	166-110	142-116	155-103
67	170-140	186-124	166-136	181-121	161-131	175-117	158-130	173-115	156-128	170-114		
68	175-143	191-127	170-140	186-124								
69	180-148	197-131	176-144	192-128								

Figures 1 and 2 present a summary of the effect of aging on the distribution of weight. The percentage of underweight, average weight, moderately overweight, and severely overweight persons at each five-year age interval is shown for men in figure 1 and for women in figure 2. These weight groups are defined in the section on methods. Among men the proportion of underweight subjects increases from about 20% at the age of 65 years to about 50% in the oldest group, while moderately and severely overweight men decrease from about 30 to about 10%. Similarly, in women the proportion of underweight subjects increases from about 20% at the ages of 65 to 69 years to 55% at the age of 90 years and over, while overweight subjects decrease from 40 to 10%. The incidence of overweight subjects decreases sharply with advancing age from 65 years onward, whereas the frequency of underweight subjects increases greatly in both sexes.

Comment

As indicated, the table of average weight for persons at each inch of height, and the table of weight range 10% and 20% below and above average, are, to our knowledge, the first of their kind to have been presented in the United States for the age group 65 to 94 years. It is based only on ambulant, apparently healthy subjects without evidence of cardiovascular or renal disease. The number of subjects, 2,925 men and 2,694 women, and the homogeneity and widespread geographical distribution of the sample are, we believe, sufficient to give it considerable statistical credibility.

While this table is the first for the older population, average tables of weight for adults between the ages of 15 and 69 years have been in existence for more than 50 years. Historically, the first of these tables for the United States, known as the Shepherd table, was compiled from a study by the Association of Life Insurance Medical Directors of 1897.[1d] The one which is in general use today was derived from the Medico-Actuarial Mortality Investigation published in 1912.[1a] In 1931 [1a] another large-scale intercompany insurance investigation was made, which indicated that the average weights observed in 1912 had not changed materially during the first quarter of this century. Except for persons aged under 25 years these findings were so similar to the existing tables of 1912 that they were regarded not as a revision but as a confirmation of the previously presented data.

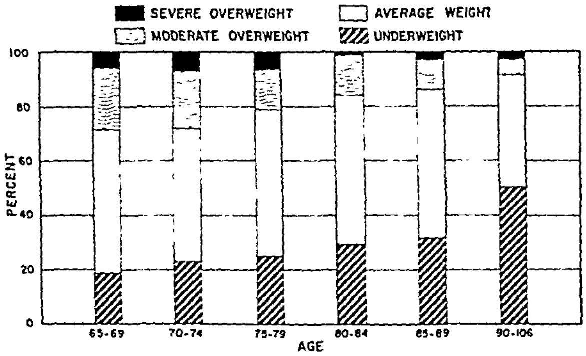

Fig. 1.—Distribution of weight for men aged 65 to 106 years.

In 1957, a height and weight table was presented by Bøe and co-workers,[6] on the basis of a survey of almost the entire adult population of the city of Bergen, Norway. While there were fewer persons aged 65 years and older than in the current study, comparison revealed an interesting observation, namely, that the Norwegian population was heavier at each inch of height than the American one reported here (as much as 7 lb. [3.2 kg.] for men and 15 lb. [7 kg.] for women). This, we believe, indicates the necessity for limiting the applications of such tables to the population sampled.

The decrease in weight with age after the age of 65 years probably can be explained as the additive result of two factors, (1) a loss of body substance, i. e., protein, water, fat, and calcium, which is the physiological accompaniment of aging[7]; and (2) a progressive reduction in the proportion of overweight subjects because of a relatively high mortality among these as compared with the "underweight." Thus, the current survey again emphasizes the favorable survival rate of thin persons.

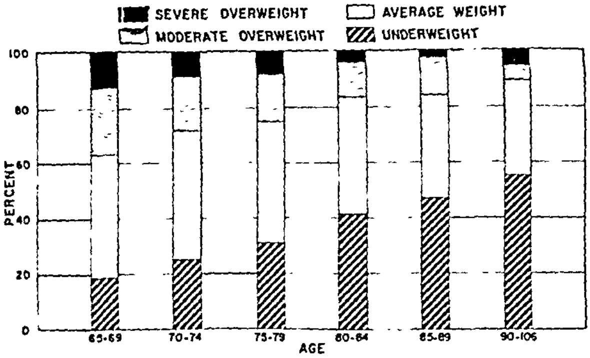

Fig. 2.—Distribution of weight for women aged 65 to 106 years.

The association of even moderate overweight with an excessive mortality rate was first clearly demonstrated by the analysis of death rates among insured persons. Shepherd,[1d] in 1897, in a paper on the relation of body build to longevity, delivered before the Association of Life Insurance Medical Directors, concluded that, as policy risks, "The overweight are clearly less desirable than either the normal or the underweight." These conclusions concerning overweight and excess mortality at ages above 28 years were confirmed by more extensive life insurance studies in 1914 and 1931.[1a] In the 15-to-28-year-old groups, underweight subjects at that time did not seem to do as well as their heavier peers because of a high mortality from tuberculosis and pneumonia.[1] Subsequent studies by Dublin and Marks,[8] Blair and Haines,[9] and McCormick [10] have shown that, in the years since 1929, with the dramatic decrease in deaths from tuberculosis, underweight persons now have the most favorable mortality at all ages, even at the younger ones. Marks [1c] of the Metropolitan Life Insurance Company in 1956 summed up these mortality investigations made since 1897 by saying that ". . . excess mortality was found consistently to be due to the early onset and relatively rapid progression of diseases affecting the circulation, the excessive frequency of diabetes in which vascular breakdown occurs earlier than in nondiabetics and of disorders affecting the liver and gallbladder. The implications of these findings with regard to the penalty of overweight are unmistakable."

It was found that height does not bear any relationship to longevity.[3] This finding contradicted an impression held by some investigators [11] and lay persons in general that tall persons do not have as satisfactory a survival rate as shorter ones.

Regarding the nature of the table of weights by height we are herewith presenting, we wish to add a note in explanation of what is actually represented and its relationship to past tables of height and weight. Our tables of weights are average weight readings which may be contrasted with tables representing "ideal weights." The "ideal weight" may be defined simply as that weight associated with the lowest mortality rate, since we have seen that excess weight and excess mortality are related. Hunter [12] pointed out that the "average" weight is not necessarily the best weight, since it merely "reflects the racial stock, the methods of life, the climate and other conditions."

Ideal weight has generally proved to be considerably less than the average weight at all ages from 20 to 65 years. While such a table of "ideal" weight has been presented for ages 20 to 65,[13] there is no comparable study of those aged 65 years and over. We hope that in the future such a study can be made of the older population. In the interim, we feel that this table can be used to guide the weight of our older population.

Conclusions

A table of average weight at each inch of height, for persons of each sex, in five-year age groups, has been presented for the population between 65 and 94 years of age. This is the first table to be constructed for this group. The current study involved apparently healthy subjects in the United States. The data should prove valuable in research on the relationship of weight to disease and as a guide for weight control in the older population. Weight increases with increasing height, as the bony frame becomes larger and heavier. After 65 years of age mean weight decreases progressively with advancing age in both sexes at every inch level of height. This decrease is due to loss of body substance and to reduction in the proportion of overweight subjects by a relatively higher mortality.

From the age of 65 to that of 94 years, overweight men decrease from 30 to only 10% of the population, while underweight men increase in frequency from 20 to 50%. At the same ages, overweight women decrease from 40 to 10%, while underweight women increase from 20 to 55%. This emphasizes the favorable survival rate of underweight persons. In the older age group, ±20% variation from the mean is too broad a criterion for normal; only a ±10% variation in weight should be considered healthy. There is little or no change in average height in persons aged from 65 through 94 years. Tall persons seem to have as satisfactory a survival rate as shorter ones.

125 E. 72nd St. (21) (Dr. Master).

Messrs. E. A. Lew, actuary and statistician, of the Metropolitan Life Insurance Company, and Richard V. Kasius, staff member of the Milbank Memorial Fund, assisted in the preparation of this report.

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IMPACT OF SPACE EXPLORATION ON BIOLOGY AND MEDICINE

Clark T. Randt, M.D., Washington, D. C.

Space exploration offers an unparalleled opportunity for the productive integration of the physical and biological sciences directed toward expansion of our knowledge of the universe. Means of improving human tolerance of the expected combined stresses involved in space flight and provision of adequate life-support systems will be necessary to allow man to lend his unique capabilities to accomplishment of the tasks ahead. New knowledge of extraterrestrial environmental effects on all forms of life will result from studies of comparative biology on the broadest scale and will undoubtedly lead to further understanding of the fundamental laws of nature.

Basic human drives for pioneering and conquest can find acceptable expression in extraterrestrial exploration. It is unmistakably clear that our civilization cannot survive a thermonuclear conflict. The expression of aggressive drives in war has repeatedly supplied an impetus for unusual increments in the growth of the arts and sciences. A historical review of intellectual progress and concomitant technological advance gives reason to expect that expanded knowledge of the universe will produce an unprecedented burst of creative activity in biology and medicine as well as in the physical sciences and engineering.

Role of Man in Space

Only with the advent of high-altitude high-speed operations within the past two decades has man's role in flight become the subject of intensive study in military aviation medicine, resulting in special adaptation of aircraft and equipment to the pilot. These developments have also brought to the fore the necessity for more discriminating selection of highly intelligent, inherently capable persons for extensive training prior to being given control of intricately designed high-powered vehicles.

At the threshold of the Space Age, questions related to man's participation in space flight and exploration have already assumed significant proportions. Suggestions have been made that reveal doubt in some quarters as to the propriety and ultimate usefulness of man's being propelled into outer space. From some of the same sources the space effort, in general, has been regarded as no more than large-scale participation in an international pyrotechnic display involving sizable sums of the taxpayer's money. The scientific, political, economic, and sociological implications of such statements are unfounded. My remarks are directed to the scientific aspects of space exploration as they relate to biology and medicine.

Initial serious interest in man's role in space has been concerned with the utilization of his unique characteristics which allow him to absorb a wide variety of observations, to process this data, to store it as memory, or to use it to exercise judgment in decision-making in a way that could not conceivably be done by any man-made device. Such human qualities as persistence and resourcefulness as well as the relative reliability of complex human systems further indicate the need for man's inclusion in the operational aspects of space flight and exploration.

Research.—Research and development designed to comply with the requirements of manned space flight are now in progress. Military aviation medical personnel are making a major contribution in this area. Their knowledge and experience, gained over the last 20 years, provide a substantial base on which to build for the future.

The immediate needs of space flight are for conquest by man, within the limits of his tolerance, of the stresses of acceleration, vibration, temperature, weightlessness, and impact during the launching, flight, and reentry phases. Life-support systems, insuring survival by maintaining the vehicle environment within physiological limits as to pressure, oxygen supply, humidity, carbon dioxide concentration, and waste removal, are essential. Means of escape in case of impending disaster must be provided. Instrumentation allowing for recording and telemetry of data concerning the function of man and these systems in flight are being further developed. These are some of the prerequisites for determining man's capability of performance which will make it possible for him to lend his unusual talents to the problems at hand. These factors must be projected into the near future when larger payloads and flights of longer duration are feasible. Regenerative systems for support of life which use solar energy to provide fluid, food, and gaseous requirements will then be necessary. Radiation hazards must be further delineated and overcome.

From the National Aeronautics and Space Administration.

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Means for management of possible meteorite damage and arrangements for in-flight maintenance of equipment over periods lasting weeks or months, or more, must be developed.

Man's nervous system is the key to his usefulness in the space setting confronting us. With the present emphasis on survival, no vital system, including the heart, circulation, or respiratory mechanism, has been overlooked, but relatively little effort has been made to assess more than the most fundamental life-supporting functions of the brain. The role of the nervous system in the rapid adaptation of the body to the internal and external environment has been established. Longer term adjustments involve hormonal influences which are also under neural control. The physiological concomitants of more complex levels of behavior and performance are little understood. One of several approaches to this problem involves intensified study of the nature of the varied input from sensory receptors.

Weightlessness and other aspects of sensory deprivation have special pertinence in anticipation of manned space flight. More information about the integration and elaboration of the afferent input as it modifies the neural substrate of abstract thought, learning, memory, and emotion is urgently needed. Perceptions are likely to be altered by long-term application of unusual forces on the body sensors, as well as by isolation, fatigue, emotional reactions, and long-duration modifications of cyclic light-dark, sleep-activity, and temperature rhythms. Study of animals and man subjected to real or simulated space environmental conditions offers a unique opportunity to gain fundamental information relating to consciousness, orientation, mentation, emotional reactions, and motor coordination.

Integration of the Sciences

A number of new problems of great complexity and interdependence relating to the fields of biology and medicine arise in anticipation of manned space flight and exploration. An unparalleled opportunity for productive integration of the physical sciences, engineering, and the biological sciences is presented and must be comprehensively exploited to produce the desired results. Such integration has been notably difficult to accomplish in the past. The traditional organization of the biological sciences is as follows: biophysics, biochemistry, physiology, and psychology. Reorganization of this as well as of the physical science and engineering disciplines, in vertical fashion, to be applied to the problems to be studied, will provide the best opportunity for bringing each discipline to bear on the major areas under investigation. Restriction of effort to immediate problems such as acceleration and other forms of stress, radiation effects, and life-support systems would not satisfactorily provide the scope or flexibility necessary for meeting the requirements of the future. Studies from a molecular to an intact organism level, where appropriate, with use of an interdisciplinary approach, are likely to be most productive.

Coordinated efforts in "bioengineering" are now in progress which are concerned with development of a suitable space vehicle environment and other life-support systems consonant with present and anticipated payload capabilities. The limits of tolerance for various physiological stresses and means of adaptation to remain within these boundaries are being determined on centrifuges, in altitude chambers, and by other flight-simulating devices. In this process, a number of technological advances related to designing vehicles to fit men and training men to use them are being accomplished.

The broad application of biophysics is relevant not only to problems of radiation and physiological instrumentation but also to the cardiopulmonary aspects of acceleration and weightlessness. Long-term results of alterations in pressure, gas exchange, humidity, and temperature are worthy of consideration. Investigations of more extensive use of computers for the processing of biological data are appropriate.

Metabolic studies are concerned with cellular division, nutritional requirements, and utilization of energy of a variety of organisms, including man. Chemical and photosynthetic processes are expected to provide regenerative systems to sustain life over long periods of time in a closed ecologic system. These closed systems introduce special consideration of intoxicants and contaminants which could be injurious to living organisms. The possible uses of controlled hypothermia are being explored with regard to reduction of metabolic requirements for food and fluid as well as protection from various stresses, including those in the psychological sphere.

Studies of extraterrestrial environments and their effects on biological adaptation and genetics are of particular interest. Botanical and zoological investigations from a microbiological level to man have pertinence to the exploitation of an entirely new dimension for the observation of biological effects.

Results.—It is not part of scientific investigation to predict the specific utility of the results. However, there is no reasonable doubt that space exploration offers a new vantage point for observation of the effects of environmental factors on all forms of life, which will provide numerous important applications of a practical nature relative to biology and medicine. Absence of gravitational force, extreme alterations in remote atmospheric composition and pressure, radiation, and other energy fields affect organisms of all degrees of complexity, including man. Development of means of measuring and surmounting certain deleterious influences will be forthcoming, which will probably be applicable to many problems we now face on earth. The unfamiliar features of this unexplored environment can be expected to serve as tools for revealing the nature of many hitherto unexplained biological phenomena. Ultimately, it is likely that extraterrestrial living organisms will be discovered as well as physical and biological resources to support life as we know it.

More comprehensive knowledge of the environment in space, on the moon, and on planets undoubtedly will have a profound influence on man and other forms of life on earth. The horizon, expanded to include progressively more of the universe, can be expected to provide intense stimulation with resultant significant advances in biology and medicine.

PHYSIOLOGICAL ASPECTS OF HYPERGRAVIC AND HYPOGRAVIC STATES

APPLICATION TO SPACE FLIGHT

Major Julian E. Ward (MC), U. S. A. F.

The planning of a circumterrestial orbiting space flight of a human passenger includes a mission profile to accommodate the inherent structural limitations of the passenger and life-supporting subsystems. During launching, reentry, and recovery phases of a man-missile flight, the man will be in gravitational environments with which he is not familiar, since the force on the earth is 1 g. Should an escape from the missile be necessary, during its powered flight (4 to 10 g), decelerating forces of 40 g will be affecting the capsule. A man can tolerate a force of 8 g for only 90 seconds. The functional problems of the human body while in orbit, a zero-gravity environment, concern neurological mechanisms, spatial orientation, motion sickness, cardiovascular function, gastrointestinal activity, excretion, and skeletal muscle activity. The value of the physician members of the space-capsule-design team is obvious, and one of the important objectives of the manned space flight will be to collect psychophysiological data.

The missile inventory of the world powers now includes vehicles with sufficient thrust to place into circumterrestrial orbit a human passenger with life-support subsystems. The United States National Aeronautics and Space Administration has announced preliminary plans for one such vehicle, Project Mercury, based on the use of the Air Force-developed Atlas booster. The planning of any such venture requires an understanding of the dynamic forces produced in such a flight and the manner in which they alter physiological function. The mission profile must be shaped around the inherent structural limitations of the human occupant. In this brief outline of the so-called hypergravic and hypogravic states which will be encountered by biological payloads, discussions will be directed toward the use of a hypothetical vehicle with intercontinental ballistic missile (ICBM) energy characteristics. A conceptual rather than a didactic approach to such stresses will be given, with estimates of human limitations for certain aspects of the mission profile.

The man-missile flight will impart other than 1-g fields to the occupant throughout launched escape from the vehicle in powered flight and orbit and during the reentry and recovery phases.

First Phases

Boost.—In order to markedly improve tolerance to accelerative forces the capsule pilot-subject will be seated with the long axis of his body perpendicular to the line of flight, thus necessitating the assumption of a prone or supine position while the vehicle is on the launch pad. Centrifuge studies by Bondurant and co-workers[1] of the Air Force Aeromedical Laboratory have revealed that, in the optimum position, the vector of force should be applied from anterior to posterior at 65 degrees to the long axis of the trunk, while the lower extremities are maintained flexed at a 90-degree angle at hips and knee. Large liquid-fuel engines characteristically impart a slow increase in acceleration until

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Chief, Biomedical Division, Air Force Ballistic Missile Division, Los Angeles. Dr. Ward is now Director, Base Medical Services, Spangdahlem A. F. B., Germany.

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a peak of usually less than 10 g is attained. An instantaneous or brief period of coasting may follow until second-stage ignition occurs, which, with liquid-fuel engines, reproduces a g-curve closely resembling that of first-stage ignition. Human tolerance to an 8-g exposure is roughly 90 seconds. Since burning time after achieving 4 g is rarely more than one minute, such lift-off accelerations are easily tolerable.

Escape.—The most hazardous portion of the entire flight may occur during the boost acceleration period. Should the engine or guidance systems, or both, fail, deceleration forces exceeding 40 g may be imparted to the capsule. Therefore, careful attention is given to the forced shaping of such an emergency trajectory by escape rockets or extendable deceleration dive flaps, or both. The most critical escape period for a two-stage vehicle is near the midburning time of the second stage.

Orbit

Once a satellite orbit has been established, the mission may require one or more rotations around the earth, which would subject the pilot to a period of "zero-gravity" varying from one and one-half hours to many days. Although interest in the phenomenon of weightlessness has virtually paralleled interest in space travel, it is only within the past decade that anything more than theoretical analysis has been attempted. During this period, experiments involving the brief exposure of biological specimens, including man, to the weightless state have been devised with use of parabolic flights by jet aircraft. Even shorter exposures have been produced and their effects studied during free falls from high towers. Finally, ballistic missiles have yielded many minutes of weightlessness for animal subjects; a relatively prolonged exposure was achieved in the canine experiment of the U. S. S. R.'s Sputnik 2.

In spite of this limited experience, we are able to foresee, to some extent, the effects and potential problems of weightlessness on biological systems and components. Also, we can foresee the requirement for the development and improvement of certain mechanical contrivances to assist man in adapting to this subjectively new milieu. The physiological parameters which may be significantly affected by exposure to a 0-g field include neurological mechanisms, spatial orientation, motion sickness, the cardiovascular and gastrointestinal systems, body waste elimination, and skeletal muscle activity.

Concern has been voiced by many medical investigators over the potential effect of sudden withdrawal of the shower of sensory impulses generated by the graviceptor transducers of the body. However, there are many other sources of "neurological background noise" which may be ordinarily blocked out by the constant flood of "1-g" body positional information pouring into the central nervous system. This sensory output from the integumental surface and viscera may substitute for the normal gravity proprioceptive sensory outpourings; training of subjects by artificial reinforcement of skin pressure clues may offer an adequate solution. Depth and restfulness of sleep under these conditions are under inquiry; drugs may be required to give restful, fatigue-relieving sleep.

Disorientation as a response to the weightless state has been reported several times under both operational and experimental situations in parabolic maneuvers. In virtually all such cases, it appears that these incidents resulted from attempts at "free float." Such difficulties are generally obviated when the subject is well restrained, with extremities resting against solid objects. However, unrestrained locomotion about a space cabin may cause some degree of disorientation. Cabin design and coloring to indicate "floor" and "ceiling" will assist in maintaining spatial orientation by visual means.

Individual susceptibility to nausea and vomiting under the relatively simple and experimentally reproducible conditions of ordinary aircraft flight is poorly understood. Any attempt to derive definitive conclusions from the complex motion situation prevailing in the production of parabolic trajectories by jet aircraft is therefore fallacious. But cognizance must be taken of the report of illness in about one-third of subjects exposed to such flight conditions. Most, although perhaps not all, of these responses may be explained by such factors as the nature of changing acceleration fields on entry and exit from these maneuvers, the flying experience of the subjects, and incompetence of the stomach's cardiac sphincter. The extent to which the weightless state alone influences the incidence of this sickness will remain in doubt until actual manned orbital flights are completed.

One interesting fact reported from the Sputnik 2 experiment was the unusual lag in return to normal of the pulse rate of the canine passenger from the tachycardia induced during vehicle boost. Some degree of overfilling of the right heart, shifts of pooled venous blood, and minor changes in electric and anatomic cardiac axes may occur, but there is no reason to believe that cardiovascular instability will result. There is certainly more basis for predicting cardiovascular symptoms in subjects thoroughly "acclimatized" to zero "g" when they return to a normal accelerative environment on earth. Von Beckh[2] has recently demonstrated that lowered positive g tolerance may result from even brief exposures to weightlessness, and this may be of great significance during a reentry maneuver after a period in orbit.

Experimental observations[3] of the deglutition mechanism under weightless conditions have indicated that with normal mastication of solids, swallowing of the semiliquid bolus of food presents no problem. Poorly chewed solids tend to present difficulty in swallowing; indeed, these particles may occasionally float above the palate, and the danger of aspiration is real.

As mentioned previously, the competence of the cardiac sphincter of the stomach under these conditions is dubious. During parabolic jet maneuvers a regurgitation of stomach contents has resulted when a blow or even pressure is imparted to the abdomen; this is most often associated with ingestion of a large volume of fluids.

Many years ago Hoelzel[4] completed a comprehensive study of the passage of inert materials through the intestinal tract in which materials with widely varying densities were surveyed. It was learned that the rate of passage of these materials was an inverse function of density. Therefore, under a 0-g field, food passage time may be slightly reduced. When one considers the length of the intestine and the surface tension of the semiliquid intestinal bolus (i. e., the opportunity for absorption), it would appear that absorption of metabolites offers no problem.

Elimination of body waste solids and liquids is a function of elasticity of vesicular and visceral tissues, voluntary muscles, sphincter action, and, to only a slight extent, gravitation. In a study[5] of 26 subjects, micturition was demonstrated to be possible in the weightless state. However, 58% of these subjects, on attaining zero gravity, noted a diminution or total absence of the sense of urgency.

Studies[6] of psychomotor performance, particularly eye-hand coordination tasks, have indicated that compensation for the loss of upper-extremity weight is rapidly learned. Manipulation of the cockpit controls and environmental components by the space pilot is therefore not anticipated to be a difficult problem. Learning new locomotion techniques will undoubtedly be more difficult because of the relatively greater mass of the lower extremities.

It is apparent that we cannot assign any scientifically supported time limitation to weightless exposures for man. Evidence presently indicates that although a few persons may consider the experience an intolerable one, most will find it welcome relief from the oppression of lift-off forces.

Reentry

Prior to initiating the reentry sequence the pilot should rotate either the entire vehicle or his seated position through 180 degrees, so that g forces of reentry will be applied in the same direction as in the initial boost phase. If the pilot does not accomplish this maneuver his g time tolerance in the range of 6-10 g will be decreased about 30%.

For enhancement of vehicular dynamic stability, high drag–low lift reentry bodies must be spun, with the spinning axis coincident with the axis of flight. The anatomic axis of rotation, the speed of rotation, and the superimposed reentry g will all affect the time tolerance for spin. The greatest tolerance for spin is achieved with the center of rotation at the heart, where, without superimposed reentry deceleration forces, 100 seconds at 80 rpm is tolerable.[7]

As the space vehicle begins to dip into the sensible atmosphere on the return voyage, the decelerative forces resulting must be again programmed so that the delicate balance between the angle of reentry, the thermal pulse, and g pulses overstress neither the heat control mechanism of the reentry body nor the structural tolerance of the man. For any given reentry body a set of curves can be derived.

During the first several moments of atmospheric encounter a new stress may be imposed by the vehicle, which may begin to tumble slowly and then, orienting itself, swing through constantly decreasing arcs of amplitude with increasing frequency. The g loads imposed on any particular organ system of the subject will be derived as functions of their distance from the vehicle's center of gravity as well as of the amplitude and frequency of the oscillation. At last the vehicle settles down for its final straight-line plunge.

Finally, the mission nears completion as a parachute is deployed and the vehicle lands on earth or water. The effect of these abrupt shocks on the human body will depend on the rate of application, magnitude, direction, and duration of the force. Stapp[8] has demonstrated with rocket-sled linear decelerators that man's tolerance is not exceeded by up to 50 g applied at 500 g per second for less than a 0.2-second duration. A more rapid rate of application, e. g., 1,500 g per second, reduces the limit of human endurance to 40 g for less than a 0.2-second duration. Therefore, parachute deployment and ground impact must be regulated by parachute design in the former and controlled structural collapse or shock absorption devices, or both, in the latter.

The value of the physician member of the space capsule design team is apparent and needs no further emphasis. The various stresses of space flight, arising from the environment of space itself and from the stresses induced by the space vehicle, may affect many organ systems, often in a complex fashion. One of the most important medical objectives of manned space flight will be to collect additional psychophysiological data so that we may further define and refine the envelopes of human tolerance, rather than remaining cognizant only of the presence of life, or the time of death, of the space crewman.

Dr. John Sellers, Space Technology Laboratory, Inglewood, Calif., assisted in the preparation of this report.

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MEDICAL ASPECTS OF AMBIENT RADIATIONS OF EXTRATERRESTRIAL SPACE

Col. Paul A. Campbell (MC), U. S. A. F.

If man is to travel above and beyond the earth's atmosphere he will have to shield himself from radiations to which he is not ordinarily exposed. Three types of radiation here described are the primary cosmic radiation, the secondary cosmic radiation, and the two Van Allen bands of high-speed particles circulating about the earth's geomagnetic equator. Beginning at about 650 km. (400 miles) above the earth, radiation of the Van Allen type reaches intensities of 10 to 100 r per hour, which would be fatal within 30 days to more than half of a number of human subjects exposed to it for two days. An important problem in space travel, therefore, is that of circumnavigating the two zones of Van Allen radiation or of devising shields within allowable weight limits.

Extraterrestrial space abounds with energies of various sorts, potential, kinetic, and electromagnetic, in quantities and intensities that tax our powers of comprehension. It can be generalized that the radiant energies of space run the entire gamut of the eletromagnetic spectrum (fig. 1), extending from the radio waves through the infrared, the visible, and ultraviolet portions, and thence through the x-ray, gamma-ray, and cosmic-ray regions. In addition there is particulate matter of a wide range of speed and energy.

The sources of the radiation can probably be best visualized if one considers our earth, its relatively thin atmospheric sheath, and its magnetic field to lie within the sun's coronasphere, being bathed in the streams of particulate matter and radiant energy emanating from its tremendous nuclear reactions. In turn, the sun and its planetary system can be considered to be only an infinitesimally small portion of the groups of many suns and systems of our galaxy, the Milky Way. Shapley[1] stated that there are 100,000 or more stars similar to our sun in the Milky Way system. Each of these suns spews its particles and radiations, some of which are in violent interplay with those of our sun's coronasphere and with those of one another. To extend this concept, our Milky Way galaxy is only one of millions of other galaxies of the expanding universe whose energies add to this almost inconceivable cosmic interplay. Huge gas clouds, with their swirling magnetic fields, within these various systems act as Gargantuan accelerators or traps, imparting greater speeds or slowing or trapping the particles and the energies, as the case may be.

The earth's atmospheric mass and magnetic fields have in the past shielded the surface of the earth and those who dwell on it, to a degree which at least renders it habitable, from these cosmic materials and energies. Only portions of the radio bands, the infrared and ultraviolet areas, and almost all of the visual range of the electromagnetic spectrum are allowed to pass through. Even these are attenuated and dispersed in varying degrees. They are necessary to life as we know it. It is interesting that man, living under the earth's atmospheric canopy, has, through scientific diligence and industry, developed electronic, photographic, optical, chemical, and other sensors capable of piercing the shield and measuring the energies of space which he cannot himself sense. The atmospheric filtering effect,

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Chief, Space Medicine Division, School of Aviation Medicine, Randolph Air Force Base, Texas.

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which has made the evolution and the existence of life on earth possible, is produced by water vapor, ozone, oxygen, carbon dioxide, and such particulate matter as smoke.[2] The terrestrial magnetic fields repel, deflect, or trap many of the energies and particles which would be hazardous were they to strike our atmosphere and our earth with unattenuated force.

Hazards for Man

As new sciences of propulsion carry man beyond the benevolent atmospheric and magnetic shield, he will for the first time be exposed to unattenuated cosmic energies and particles and will be required, through his own ingenuity and resources, to furnish substitute shielding or a substitute for shielding. His ability to shield himself effectively, or possibly to avoid the energies and particles through artful navigation or repulsion, will be one of the most important final determinants of human participation in space operations.

Examining the electromagnetic spectrum from the viewpoint of extra-atmospheric operations (fig. 1), the areas of longer wave lengths embracing the radio waves seem to have no biological significance until the infrared or heat frequencies are approached. The unattenuated heat of the sun striking the exposed half of a space vehicle would, under proper circumstances, heat the surface to something approaching the solar constant of 1.94 calories per minute per square centimeter, while the unexposed shadow side would be in an area approaching absolute zero. However, in space, temperature as such loses its significance, since there is no atmospheric transmission of heat. Experience with the satellites has demonstrated, however, that proper coating of the surfaces can attenuate the temperature effects sufficiently to hold the interiors within a habitable range. Properly controlled heating and air conditioning which would not represent prohibitive weight could then carry the crew compartment into the comfort range. According to Hibbs,[3] satellite shell temperatures in the missiles Explorer 1 and 2 ranged from —25 C (—13 F) to 75 C (166 F), while the interior was held to a range between 0 C (32 F) and 35 C (95 F), a habitable range.

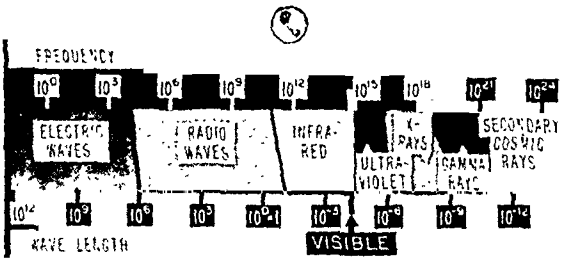

Fig. 1.—Electromagnetic radiations of space: electromagnetic spectrum. Wave lengths are given in centimeters; frequency is in waves per second.

The great heat of the sun's rays unattenuated by the atmosphere of the earth will, through the use of solar heat generators, possibly give us an important energy source, especially for space stations or extraterrestrial colonies. Through this abundant energy source the soil of, let us say, the moon, might be cracked into its basic constituents, among which we hope are oxygen and either water itself or the constituents of water. This energy might also be used in the breaking down of urine and its reconstitution into usable water, as well as the incineration of fecal material into usable materials.

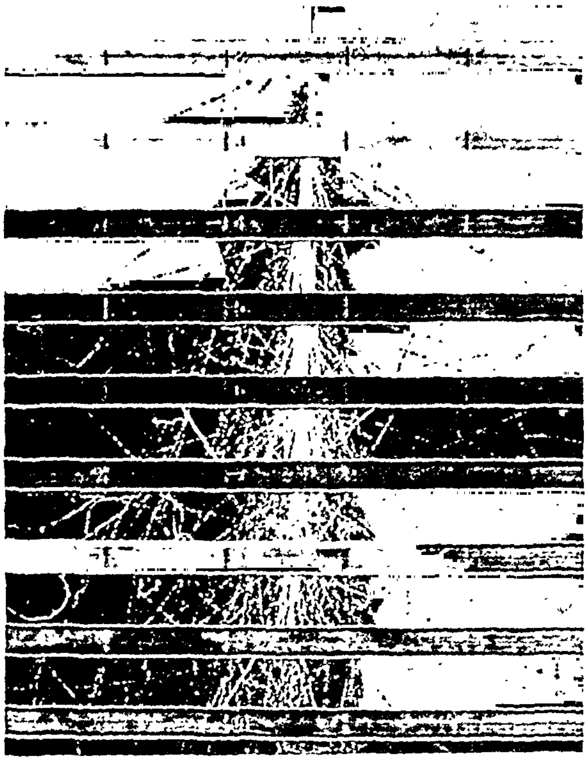

Fig. 2.—Effect of cosmic primary passing through layers of lead 0.5 in. in thickness, showing what happens when particles collide. Cosmic ray enters at top, strikes lead plate, and creates shower of high-energy electrons, simulating reaction as it occurs in space.[4] (Reprinted from *Think*, with permission of author.)

The visible and ultraviolet area of the spectrum can be adequately shielded against by proper choice of window materials and the types of shielding which would be inherent in a well-designed space vehicle. However, there will be a new visual experience to cope with in that all reflecting surfaces will, in proportion to their reflecting ability, reflect the more or less unattenuated light of the sun, and, in the case of exterior reflections, this will be against the black background of space. Light adaptation here will be a factor. Brightness contrasts as high as 1 to 60,000 may be present above the atmosphere.

Portions of the visible light band are necessary for the process of photosynthesis. This process may some day be important as a biosynthetic gas ex-changer and may use algae and plants to take the astronaut's expelled carbon dioxide and convert it into oxygen. In this process starch is manufactured and multiplication of the algal cells or growth of the plants occurs. The simplified chemistry is as follows.

$$CO_2 + H_2O + \text{radiant energy} \rightarrow \text{starch } (C_xH_xO_x) \text{ or sugar} + O_2$$

Weight and capacity restrictions may curtail the use of biosynthetic gas exchangers to space stations or such colonies as a lunar colony. The state of this aspect of science is rapidly improving and may some day be important to us in the achievement of the exploration of space.

Problem Areas

The serious biological problems begin to occur as we enter the areas of higher frequencies and of shorter waves and the various phenomena resulting from the rest of the spectrum, since simple shielding here is no longer effective. Our knowledge is still incomplete in this range, and opinions are, for the most part, conjectures. In the light of present knowledge—and it must be pointed out here that our knowledge is changing from day to day, almost from hour to hour—it seems that three areas can be identified: the so-called Van Allen type of radiation, the cosmic secondaries, and the cosmic primaries. These cannot be identified as discrete spectral areas but they can be identified as discrete problem areas. For purposes of explanation it would be best, at this point, to depart from the spectral order and discuss cosmic primary radiation.

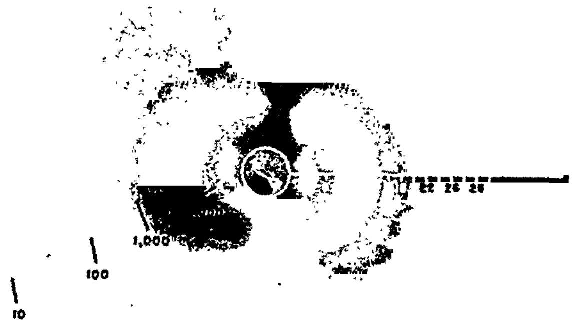

Fig. 3.—Van Allen radiation belts. Horizontal scale at right is in miles of altitude. Diagonal scale to left is in counts per second registered by Geiger counters on Pioneer. Data and adaptation from Van Allen.[8]

Cosmic Primaries.—The cosmic primaries appear to be a mixture of stripped-down atomic nuclei, ranging from protons through iron (z.=26) and possibly even heavier elements. The various nuclear species appear to be present in the flux of particles in proportion to their relative abundancies in the universe.[4] They possess energy measured in billions of electron volts, and the particles are capable of producing nuclear disintegration. Secondary rays, tertiary rays, and mesons are produced by impact with our atmosphere or other material. A remarkable example[5] has been photographed by Prof. Bruno Rossi of the Massachusetts Institute of Technology (fig. 2), showing a hit penetrating a series of 0.5-in. lead plates in a cloud chamber. There are still gaps in our knowledge of the biological effects of primary cosmic particles, but it is believed that they act similarly to radiation of the alpha-particle type, with quick energy dissipation and resultant high concentrations of ion pairs along short tracks.

Primary cosmic particles are repelled or deflected by the earth's magnetic field, and consequently the number striking the atmosphere or the surface of the earth varies greatly with geomagnetic latitude. The greatest geomagnetic attenuation effect is thus in the equatorial regions, while the least is in the areas of the magnetic poles. The energy required to penetrate the equatorial field is greater by a factor of 4 to 6 than at latitude 60 degrees north. Thus one must assume that orbital travel in the vicinity of the earth, crossing the magnetic poles, will be more hazardous from the standpoint of cosmic primaries than it will be at equatorial orbits. As will be pointed out later, this is almost the exact antithesis of the situation produced by the Van Allen type of radiation.

Just how serious is the primary cosmic ray hazard? Much study has been devoted to the realistic assessment of the hazard by Schaefer,[4] Shepherd,[6] Simons,[7] Eugster,[8] and many others. An assessment must consider the statistical distribution of hits. Some areas of the nervous system, the genetic system, or the lens of the eye may be more vulnerable than others. The duration of flight, the distance factor, and the geomagnetic orientation of the flight all have bearing, as do such factors as the type of shielding, solar flare activity, and atmospheric density. The matter is extremely controversial, but I believe the consensus is that primary cosmic radiation will probaby not limit human participation in space flight of the type and extent we may visualize in the readily foreseeable future.

Secondary Cosmic Radiation.—Secondary cosmic radiation results from the effects of the heavy primaries, with their huge energies, striking air particles at the top of the atmosphere and producing cascades of radioactive rubble. For purposes of this discussion, which must be limited to the biological problems of space travel, the secondaries produced by interaction with the atmosphere can be glossed over rather lightly, since their major distribution is limited to altitudes between 60,000 and 90,000 ft. which will be penetrated so rapidly during both flight exit and reentry as to pose no serious problem.

Van Allen Type of Radiation.—This, then, brings us to our final enigma, the intense bands of so-called Van Allen type of radiation. Although previously predicted by a few, it was only brought into sharp focus by the measurements "beeped" back by the Explorer satellites 1, 3, and 4, and confirmed by the Pioneer 1, 3, and 4. At the time of the writing of this paper, knowledge remains scanty. There appear, however, to be two bands of high concentrations of high-speed electrons or protons, or both, circulating about the earth's geomagnetic equator (fig. 3). They are believed by most of the Van Allen group to be particles of solar origin, trapped by the earth's electromagnetic field and varying with solar eruptions. Some investigators, however, feel that particles in the inner belt may be produced by radioactive decay of neutrons, resulting from an interaction between cosmic radiation and the materials in the top of the atmosphere. Van Allen's[9] tentative explanation is something like this: The particles originate in the sun and in some manner are injected into the earth's magnetic fields, where they are deflected into corkscrew-like trajectories around the lines of force and trapped. As they spill over in the auroral zones they produce auroras, magnetic storms, and related phenomena. They may produce air glow and may account for some of the high temperatures noted in the upper atmosphere.

Measurements indicate maximum radiation levels to be between 10 and 100 r per hour, depending on the so far undetermined proportion of electrons and protons. A human being exposed for two days at a rate of 10 r per hour would, according to many figures, have only about an equal chance for survival.

In conclusion, there do appear to be corridors which could be traversed in orbital flight, since, according to present data, there seems to be an envelope above the sensible drag of the atmosphere, above about 140 miles, yet under the serious concentrations of Van Allen-type radiation beginning at about 400 miles. Man probably could travel in this area, providing his orbit approached an ideal circular configuration. From the standpoint of escape into the outer reaches of space, the corridor of minimum Van Allen-type radiation is almost exactly that of the maximum concentration of primary cosmic radiation. Whether or not such orbits could be fitted in to our present patterns set up by propellant energies, "g" tolerances, and celestial mechanics, is an outstanding question, as is the problem of shielding within allowable weight restrictions. Those of us interested in space travel, however, are noted for optimism.

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BACTERIAL PRODUCTS CAN SUPPRESS MULTIPLICATION OF VIRUS IN TISSUE CULTURES.—We have observed on numerous occasions a suppression of virus production in tissue cultures treated with bacterial filtrates. In these instances the filtrates have produced no visible change in the cultures and the cytopathogenic effects seen after infection with virus have not differed from those observed in control cultures. We do not therefore think that the inhibitory effect which we have observed is due to a crude "toxic" effect on the cells of the monolayers. It was shown experimentally that the filtrates tested did not have a direct inactivating effect on the free virus of the tissue culture fluids. Furthermore, in none of the experiments could we find evidence that the attachment of virus to the cells was prevented. It would appear, therefore, that the endotoxin filtrates affect virus multiplication within the cells. Sterile crude filtrates of the normal bacterial flora of 2 out of 3 persons tested suppressed the growth of poliovirus in monkey kidney tissue cultures. The active principle was found to be present in 3 out of 4 strains of Bact. coli isolated from one of these persons. Partly purified endotoxin of Salm. typhymurium produced the same effect to a much higher degree.—M. Likar, E. O. Bartley, and D. C. Wilson, Observations on the Interaction of Poliovirus and Host Cells in Vitro: III. The Effect of Some Bacterial Metabolites and Endotoxins, *The British Journal of Experimental Pathology,* August, 1959.

PSYCHOPHYSIOLOGY OF HYPNOSIS

Louis J. West, M.D., Oklahoma City

The theory of hypnosis here formulated postulates certain psychophysiological mechanisms, especially the ascending reticular activating system, through which interpersonal and intrapersonal forces operate to achieve and maintain the hypnotic state. From this theory it can be predicted that certain drugs, such as the phenothiazine derivatives, will render the chronically anxious patient more accessible to hypnosis whereas certain others, such as phenobarbital, will not. These predictions are in accord with the author's experience.

There are many reasons for assuming that the hypnotic state is essentially a controlled dissociative reaction.[1] However, this view requires a broader model of the psychophysiology underlying the process of dissociation than has hitherto been formulated. A stereotyped presentation appears in many standard textbooks, with definitions that are virtually identical with Janet's original ones, giving only a limited concept of the mechanisms involved in dissociation and their role in normal as well as abnormal psychological functions.

The four classic dissociative reactions are fugue, amnesia, somnambulism, and multiple personality. However, the dissociation from awareness of sensory phenomena (seen in conversion hysteria or in hypnotic anesthesia), the dissociated experience of sensations or feelings without appropriate external or internal stimuli (as in hallucinations, *déjà vu*, or feelings of unreality), and certain episodes of unusual behavior seemingly beyond conscious control are frequently accepted within the framework of modern dynamic psychopathology as dissociative phenomena.

In the past 10 years an increasing fund of data concerning the physiology of awareness has made it possible for us to see the clinical dissociative reactions as pathological exercises of certain normal brain mechanisms. Whatever one may choose to call these mechanisms (perhaps "parassociative" would be an appropriate term), they subserve the functions of scanning and screening information and regulating the sphere of awareness moment by moment. Only a minute portion of total available information—from the external environment, from within the body, and from the brain's own enormous stores—can be held in awareness at any given time. Concentration, reality-testing, and simple survival require the exercise of scanning and screening mechanisms to keep the searchlight of awareness focused on selected areas of psychic content and to keep everything else out of awareness.

Theoretical Considerations

Weitzenhoffer[2] recently defined hypnosis in terms of a "dissociation of awareness from the majority of sensory and even strictly neural events that are taking place." This definition implies an appreciation of the combined functions of focus and exclusion, or of a balance between excitation and inhibition, which is shared by the psychoanalytic theories[3] of hypnosis on the one hand and the Pavlovian[4] on the other. But such a "dissociation of awareness" characterizes not only hypnosis but all of the classically defined dissociative reactions. It also covers the more recently defined clinical dissociative phenomena as well as dreams, hypnagogic states, sleep paralysis, "highway hypnosis," trances and ecstasies in mystical and religious rites, "fascination" or "fixation" in flyers, daydreaming, and many other mental phenomena, including the exercise of normal concentration at all levels of intensity. The "majority of sensory and neural events" are probably always excluded from consciousness at any given time in a normal person.

Apparently a sufficient amount and variety of sensory input is required to maintain the exercise of the parassociative mechanisms in relation to current external reality. In prolonged monotony, or in artificially produced sensory isolation or sensory deprivation such as described by Hebb,[5] Lilly,[6] Shurley,[7] and others, the diminished input of sensory information in the presence of continued alertness permits an increasing awareness of the brain's previously recorded perceptions. These, being released into consciousness and woven into scenes or invested as symbols by psychodynamic forces, are then perceived as images or hallucinations.[8] During those periods of sleeping in which cortical arousal increases without significant increase in appreciation of environmental stimuli, a basically similar phenomenon occurs and dreaming takes place, as Dement and Kleitman[9] have shown.

Elsewhere a conceptual model has been formulated to account for dreaming and all hallucinatory experience in terms of released perceptions.[8] This

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Professor and Head, Department of Psychiatry, Neurology, and Behavioral Sciences, University of Oklahoma School of Medicine and University Hospitals.

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model includes a consideration of the role of fatigue or input-overload of the sensory systems, as in sleep-deprivation; the blocking or poisoning of the sensory systems by drugs such as *d*-lysergic acid diethylamide (LSD-25), which distort perception and also stimulate the diencephalic centers regulating arousal; the differential chemical effect on sensory and arousal systems in the person going into and coming out of anesthesia; and the deliberate or unconscious withdrawal from or narrowing of focus on the sensory environment in the schizophrenic, the mystic, the hysteric, the hypnotic subject, the pilot concentrating on his altimeter, or the father of a family concentrating on his newspaper.

Role of the Reticular Formation

Does the brain have a definable system to permit an infinitely variable integration of incoming information on the one hand and awareness on the other? A structural basis for such a function may now be postulated. In 1942 Morison and Dempsey[10] described a nonspecific thalamocortical projection system. This was followed in 1949 by the classic paper of Moruzzi and Magoun,[11] defining some of the functions of the ascending reticular activating system. At about the same time Jasper[12] noted the relationship of the thalamic reticular formation to the previously described thalamocortical projection system. Further discussions by Magoun,[13] Lindsley,[14] MacLean,[15] and others clarified many of the regulating functions subserved by the ascending reticular activating system. It soon became apparent that the integrating effects of this extraordinary network involve not only sensory information and arousal or alertness but also emotions, memories, and transactions between neocortical and paleocortical structures.

At the present time it seems fair to say that the ascending reticular activating system integrates the relationship between sensory information and awareness. Together with the diffuse thalamocortical projection system it permits both general arousal and attention to discrete stimuli. Feedback systems from the cortex, both stimulatory and inhibitory, have recently been described. The differential functioning that is now known to be possible within the total activity of the reticular formation, whereby stimulation, inhibition, arousal, and depression can be reciprocally exercised simultaneously in different areas, makes it possible to comprehend the anatomic basis for the screening and scanning functions which must exist.

In the 10 years that have elapsed since the first paper on the ascending reticular activating system came from Magoun's laboratory, sufficient information has been compiled about its activities and interrelationships to appreciate how it subserves the reality-testing functions of the ego. When there occurs a marked narrowing of focus of awareness on a particular aspect of reality, to the exclusion of much of the rest (as in the initiation of the hypnotic trance), then sensory data (verbal suggestions) taken in through an open channel (rapport) become effective because they are not subjected to ordinary reality-testing.

The reticular activating system will maintain arousal while inhibiting appreciation of a considerable degree of reality under two circumstances that can be demonstrated in the laboratory. The first circumstance is one in which attention is fixed by a narrow range of stimuli, monotonously presented. The relatively gradual but definitely progressive decrease in reactivity to other stimuli under these circumstances can be demonstrated behaviorally in man as well as in lower animals under certain conditions. The other circumstance under which the reticular activating system functions in this manner is in the presence of an input-overload. When arousal is already high (because of strong emotion or vigorous stimulation, or both, simultaneously via several sensory modalities) feedback mechanisms cause the functional nonacceptance of nearly all additional incoming information, regardless of its significance under ordinary circumstances of adaptation.

Clinical Correlations

The experienced hypnotist will recognize these two psychophysiological situations as the most probable concomitants for the two characteristic clinical situations in which hypnosis may be easily induced: the gentle, monotonous, object-focused laboratory technique on the one hand and the emotion-laden, high stimulus–input stage technique on the other. The first is near the hypnagogic point with a low level of arousal but an even lower level of effective input; the second is near the point of spontaneous dissociative phenomena under conditions of great arousal and impaired effective input, due to input-overload's figuratively "jamming the circuits."

Between these two extremes, at the point of maximum conscious influence on reticular-formation activity, deliberate exclusion of external stimuli may be achieved through intense concentration. It is probably in this way that the trained subject quickly enters the trance state on receiving his previously defined signal from the hypnotist. Kubie and Margolin[3] formulated a theory of the psychodynamics of the relationship between hypnotist and subject that permits the trance to be induced. The theory here formulated postulates the psychophysiological mechanisms through which interpersonal and intrapersonal forces operate to achieve and maintain the hypnotic state.

Since the normally operative parassociative and integrative functions subserved by the ascending reticular activating system are fundamentally involved in hypnosis, the continuity of the hypnotic state with normal states of concentration is easily seen. This can blend into hypnagogic reverie on one extreme and into agitated arousal with spontaneous dissociations on the other. Thus it might be expected that older reports of normal waking electroencephalographic tracings of patients in the hypnotic state might be modified by the discovery of both hyperarousal patterns and drowsy patterns bordering on genuine sleep existing in patients under certain conditions of hypnosis. Recent observations indicate that this is indeed the case. The psychophysiological theory expounded here, wherein the state of arousal is seen to be less important than the relationship between arousal and effective sensory input, permits us to comprehend the maintenance of hypnotic rapport under a variety of electroencephalographic conditions. It also permits us to understand differences in autonomic responses to stimuli as well as in subjective appreciation of them.[16]

Hypnosis and Drugs

Similarly, the frame of reference provided by this theory permits a better understanding of the relationship between the actions of various drugs and the induction and maintenance of the hypnotic trance. No drug can be evaluated for its adjunctive value in the induction of hypnosis without first considering the [illegible] state of the subject at the tim[illegible]eing just right for the induction of hypnosis, will enter the trance easily, without the use of drugs. A drug administered under these circumstances (e. g., thiopental [Pentothal] sodium given intravenously to a soldier with an acute dissociative reaction in combat) may appear to be quite effective, when in actuality hypnosis is occurring, because of the psychological effect of the injection on both subject and operator, and perhaps in spite of the neuropharmacological effect of the medicament.

The patient who is chronically anxious may be rendered distinctly more accessible to hypnosis by the use of a drug which decreases central autonomic reactivity while maintaining a good cortical arousal pattern. In my experience this is borne out by the fact that phenothiazine derivatives can be helpful in such cases, whereas phenobarbital (which depresses arousal) usually is not. On the other hand, in a patient in whom tension is prominent, with manifestations chiefly in the musculoskeletal system, a barbiturate or meprobamate preparation may be helpful. Although such stimulants as amphetamine and methylphenidate have seemed to make hypnosis more difficult to induce in certain patients, they may help, when combined with barbiturates, to ease the induction of hypnosis in tense, depressed persons.

If hypnosis is seen as a controlled dissociated state, or a special state of concentration maintained through the parassociative mechanisms mediated by the ascending reticular activating system, it might be expected that drugs which cause spontaneous, pathological, dissociative phenomena to appear would at the same time render difficult or impossible the maintenance of a hypnotic trance. This has been true in my experience with the effects of LSD-25, even though the subject under its influence may be more suggestible. On the other hand, protective or reassuring hypnotic suggestions made prior to the administration of LSD-25 appear to help the subject to withstand the disorganizing and frightening effects of the drug.

Summary

Psychophysiologically, the hypnotic trance may be defined as a controlled dissociated state. This state of altered awareness is maintained through "parassociative" mechanisms mediated by the ascending reticular activating system. These mechanisms probably involve the thalamocortical projection system, corticofugal systems both excitatory and inhibitory, and other integrated regulatory systems known to function in connection with the ascending reticular activating system. When the subject is in the hypnotic state, alertness is maintained relative to the inhibition or exclusion from awareness of considerable amounts of incoming information that would ordinarily be consciously perceived in the process of reality-testing. Under these circumstances the information inserted into the restricted area of the subject's awareness by the hypnotist, through his suggestions, is accepted as reality to a greater or lesser extent, depending on the subject's dissociation of other information from awareness, moment by moment. Recently observed bioelectric variations during the hypnotic state, as well as differing reactions of hypnotic subjects to drugs under various circumstances, are compatible with this theory, which is formulated primarily to stimulate further discussion and research.

800 N. E. 13th St. (4).

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TECHNIQUES OF HYPNOSIS

William S. Kroger, M.D., Chicago

Methods for inducing formal hypnosis are classified as direct or authoritarian, indirect or permissive, and mechanical. Preliminary tests determine a patient's susceptibility to suggestion and help to decide which method to use. The subject must understand that hypnosis is not sleep and that he will be more, not less, acutely aware. He must understand that he himself induces the hypnotic state and that the operator is only acting as a guide. This "patient-centered hypnosis" differs greatly from the outmoded and dramatic authoritarian methods of the 19th century. Methods of induction are readily learned; the real problem is what to do after that.

Nearly all modern techniques for inducing hypnosis depend on a favorable "mental set" produced in the subject. This attitudinal change is brought about by misdirection, belief, confidence, and expectation—all catalyzed by the imagination. Therefore, the elicited sensory and motor responses are phenomena which are based on the subject's conviction. Conviction of hypnosis leads to hypnosis. Actually, no one really hypnotizes another person. It is, indeed, a wise hypnotist who knows who is hypnotizing whom.

Hypnosis is more readily induced if the patient knows what to expect, especially if all popular misconceptions are removed a priori. If misdirection (a ritualistic or even a formal hypnotic induction procedure) is employed, susceptibility to suggestion is also enhanced. Any technique which obscures the fact that direct suggestion is being used is misdirection. The essential ingredients for hypnosis are present whenever a highly motivated person receives prestige suggestions from a person in an authoritarian position.

Methods of Induction

In general, even though variants are used, most methods for inducing formal hypnosis belong to one of the following groups: the direct or authoritarian, the indirect or permissive, and the mechanical techniques. All utilize ideomotor and "ideosensory" conditioning. The latter term refers to the development of sensory images or percepts. These are meaningful impressions which may be evidenced by positive or negative hallucinations. Such perceptual alterations can be produced by tactile, olfactory, visual, gustatory, or auditory stimuli. For instance, "seeing" the image of one's beloved in the flames of a fireplace is a positive visual ideosensory hallucination.

The "disappearance" of the audience to a deeply hypnotized subject is an example of a negative ideosensory hallucination. Ideomotor activity refers to unconsciously produced muscular actions; an excellent example is the "back-seat driver" who "steers" the swerving car by bending in the opposite direction.

Direct.—All methods of direct induction depend on eye-fixation, with resultant fatigue and relaxation of various muscle groups, first small and then large. Utilization of ideomotor and ideosensory

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activities is as follows: "If you really wish to become more and more relaxed, just stare at the ceiling and you will notice that your eyelids are getting very, very heavy (ideosensory), indicating that you wish to close your eyes." Subjects are not aware that the eyelids get heavy and blink because of physiological factors; they attribute the tired, drowsy effect to the hypnotic technique—another form of misdirection.

Other direct techniques begin with eye closure. The suggested ideosensory and ideomotor activities motivate the subject and increase the depth of hypnosis. A rapid and direct method based on ideomotor and ideosensory conditioning is called the coin technique. In this technique the subject's thumb is used as a fixation point. Instructions are given that, at the count of three, two things will happen: the eyes will close tightly and at the same time the fingers, which tightly clasp a coin, will open and allow the coin to drop. The sound of the coin hitting the floor will be a signal that the eyes are closed tightly. At the moment of eye closure the outstretched arm is lightly stroked to produce limb catalepsy or rigidity, a sign that a medium stage of hypnosis has been reached. To insure success, instructions to close eyes and simultaneously allow the coin to drop can be repeated several times.

Indirect.—Methods of indirect induction make use of visual sensory imagery, as in the blackboard or escalator techniques. Sensory imagery techniques, in which a television or motion picture screen is imagined in the mind's eye and then utilized for hallucinated material, are best for children because of their vivid imaginations.

Visual Imagery Technique: The patient is told, "Close you eyes and relax comfortably. That's fine. Relax all over. If you will, please imagine the most comfortable chair in the world. Do you see it? (Pause and obtain response.) Soon it will be occupied by another person. Describe that person to me. (Wait for response.) Would you be willing to help me teach 'X' (person described by subject) how to go into hypnosis?" Obtain an affirmative response. Then the verbalization for a slow involuntary lifting or levitation procedure is used. The patient is interrogated about the responses that the hallucinated "subject" makes and is asked to encourage the subject to "see" the other's responses. The patient's own motor activity simulates the subject's. As he himself responds to those suggestions ostensibly made to the hallucinated subject, the shift is gradually made from the subject to the patient, until hypnosis has been accomplished.

Included in indirect methods are disguised or hidden techniques which achieve relaxation through the misdirection of taking the subject's blood pressure. As cuff pressure is released, the operator remarks, "As your blood pressure drops, you become more and more relaxed." Indirect hypnotic techniques require more active participation of the subject; in the direct approach the operator or hypnotherapist does all the work.

Mechanical.—Mechanical techniques employ repetitive visual, auditory, or tactile stimuli produced by any one of a number of devices. These consist of a metronome, whirling disks, and electronic instruments which rhythmically emit flashes with or without verbalization techniques. It has been postulated that photic "driving" of the alpha wave might induce a drowsy or dissociated state of greater receptivity to suggestions.[1] Kroger and Schneider[2] recently described an instrument called the brain wave synchronizer, an electronic device which, when used with a standard verbalization technique, induces various levels of hypnosis, possibly by photic stimulation of the brain waves. The instrument can be used alone or combined with a tape recording of the therapist's induction and dehypnotization techniques. This apparatus has helped to induce light to deep hypnosis in a high percentage of subjects. Naturally, a response is more readily effected if a favorable "mental set" is created. To some extent the expectant attitude resulting from the structured situation enhances the effectiveness of the instrument. However, about 30% of subjects who did not receive an explanation of hypnosis, nor have any knowledge that the brain wave synchronizer could induce the hypnotic state, were hypnotized to the degrees mentioned. The apparatus can deepen the hypnotic level and also speed up induction, often a time-consuming procedure, especially in refractory persons. An important advantage which eliminates apprehension is that no physical contact with the patient is required.

Conditions for Successful Hypnosis

The unsophisticated operator can determine a person's susceptibility to suggestion by various preliminary tests. For this purpose the hand clasp and postural sway tests are rapid and simple procedures. In the first, suggestions are given that the hands are tightly locked and cannot be parted. If there is difficulty or a time lag in separating the clasped fingers, this usually indicates ready hypnotizability. In the second, if the subject sways backward toward the operator in response to such suggestions, positive susceptibility is present, whereas even a slight forward swaying is presumptive evidence of resistance.

Generally, intelligent persons who can concentrate and who are highly motivated make the best hypnotic subjects; exhibitionists are, with the exception of those who use resistance as an attention-getting device, easy to hypnotize. Imbeciles, morons, and psychotics are difficult, if not impossible, to hypnotize. Those who are extremely analytical of the operator's suggestion are not good subjects. For this reason, it is necessary to employ some type of misdirection to get the subject's attention diverted to other percepts. Psychoneurotics who need hypnotherapy are more difficult to hypnotize than are those who volunteer for entertainment hypnosis; the latter have "nothing to lose" nor have they any symptoms to give up. Neurotics seldom relinquish symptoms which fulfill a definite need in their emotional make-up. Although the optimum age of a subject for hypnosis is over 8 years, it can be induced in persons from about the age of 6 years to old age.

If the subject's attention is concentrated on the suggestions of the operator, then an appropriate response is more readily obtained. Since hypnosis is a subjective and naturalistic phenomenon, it is imperative to have the subject's confidence. Conviction of hypnosis leads to hypnosis. An ungarbled message is generally received whenever a pipeline of communication is established between two persons. Attention is focused if "noise" or "static" on the "circuits" is eliminated. The factors which determine conviction depend on the attitude of the subject, the prestige of the operator, and the strength of the interpersonal relationship.

A healthy rapport is necessary for establishment of hypnosis. Naturally, the rapport is influenced by the emotional resistances of the subject as well as by the feelings and actions of the operator. These transactional processes involve many interrelated and overlapping forces within the total field of human behavior which are beyond the scope of this discussion.

The decision to employ permissive or authoritarian techniques depends on the personality of subject and operator. All therapists must be capable of switching from one approach to another, even during the same induction. Generally, passive persons respond to authoritarian techniques while subjects with dominant personalities do better when a more permissive approach is used. Persons insusceptible to either of the above methods frequently may be hypnotized by mechanical means.

Regardless of the method used, every good operator must be aware of such fundamental principles of hypnotic induction as never "losing face," promising results which may not be fulfilled, nor offering premature challenges. Subjects who are unable to respond to the suggestions of the therapist must be "given a way out." Suggestions for the subject's benefit and in accord with his wishes are more likely to be acted on because a critical attitude is not mobilized. Successful hypnotic response will be proportionate to the subject's cooperation. Motivation for hypnotic induction can be enhanced if the hypnotherapist emphasizes that the simple, elementary suggestions must be sequentially followed in order for the subject to benefit from the posthypnotic therapeutic suggestions. This places the onus or responsibility for entering hypnosis on the subject. Since everyone has a varying capacity to respond to verbal, nonverbal, intraverbal (intonation of voice), and extraverbal (implied meaning of words) suggestions, nearly all persons can achieve some degree of hypnosis.

The misconceptions which must be removed are feelings on the part of the patient that he will become unconscious or asleep, surrender his will because of "weak-mindedness," fail to "wake up," become comatose, or babble and reveal shameful secrets, as one might under anesthesia. Subjects should be informed that they cannot be made to violate their moral codes and that suggestions contrary to their wishes usually will not be followed.

Physician hypnotherapists should never use posthypnotic suggestions for their own ego-aggrandizement. The stage hypnotist or unsophisticated operator usually "plays God" with hypnosis because he thinks he has a special kind of "power." Actually, the subjects of the stage hypnotist are hypnotized even before they volunteer, because of their expectant attitudes.

The most common misconception is that hypnosis is sleep. Many deeply hypnotized subjects state, "Doctor, I am sure I was not hypnotized, I heard everything you said." Therefore, all subjects must be told that they will be more, not less, acutely aware. Actually, the purpose of the hypnotic state is to produce a hyperacuity of all the senses so that more attention is directed to the operator's words; thus, sensory and motor responses are carried out with literalness or "pinpoint" precision. Hypnotic response is further facilitated by making the subject comfortable and eliminating all distracting influences; a soundproof room free from interruptions helps to promote relaxation.

Confidence is essential, since all subjects, on the basis of subliminal cues, pick up any insecurities and hesitancies in the operator's verbal, nonverbal, intraverbal, and extraverbal suggestions; therefore, he should approach every induction with full expectation of success. Subjects readily recognize the experienced operator, and conviction of success based on his positive approach enhances cooperation and facilitates induction. There can be no modicum of success in the absence of conviction and cooperation.

Properly motivating the subject by pointing out how positive, constructive, healthful conditioning can neutralize negative, destructive, and harmful influences often eliminates conscious resistance to hypnosis. Further resistance to acceptance of suggestions results whenever, as mentioned, critical attitudes are mobilized. Therefore, suggestions must be fully in accord with the patient's needs. Patient negativism generally is due to faulty use of suggestion and improper motivation. Here, too, the inexperience of the operator affects the subject's susceptibility to suggestion. Hence, clarity and simplicity in the giving of suggestions enable the subject's imagination to respond according to the wishes of the operator. To minimize failure, subjects should also be instructed that the harder they deliberately will themselves to follow suggestions, the more difficult it will be to do so. It is axiomatic that, whenever the will and the imagination come into conflict, the imagination wins out. Hence, successful induction of hypnosis requires the subject's imagination to be involved in as many ideosensory and ideomotor responses as possible. This is readily attained by having the subject believe or imagine that his body is becoming heavy.

Monotonous repetitive stressing of such key words as "heavy" and "relaxed" narrows the field of awareness so that the subject's ability to concentrate is increased. Building up ideosensory and ideomotor responses, first by simple suggestions and then by more complicated ones, limits voluntary movement and is conducive to hypnotic relaxation. For instance, "With every breath (ideomotor) you take, and every number you count backwards (ideosensory), you will become more and more relaxed." I never use the word "sleep" in my induction technique unless the term is qualified by saying, "You will become more and more relaxed and sink into a sleep-like state, yet you will hear everything I say." Although many hypnotherapists use the term "sleep," confusion is created unless this phrase is qualified. Reinforcing a psychological suggestion (ideosensory) by a physiological effect, like lightly stroking a limb (ideomotor), further facilitates the subject's acceptance of suggestions. These suggestions must be given slowly, and sufficient time must be allowed for their assimilation.

Problems with the Hypnotic Subject

Negative conditioning, such as telling the subject he is difficult to hypnotize, is harmful. Rather, positive conditioning—that he did very well for the first time and that he will do better the next time—facilitates future inductions. Fearful subjects should never be traumatized by too early testing for anesthesia. One must be certain that the phenomenon has occurred. Fear over failure to enter hypnosis and anxiety can be allayed by a confident, sympathetic, and reassuring approach rather than a condemnatory one. Blaming the patient for his inability to enter hypnosis only creates further resistance.

Many resistant persons have a skeptical and analytic attitude. In some, overcooperation is a defense against being hypnotized. Others are merely curious or are unable to concentrate because of tensions associated with being hypnotized. All these factors decrease rapport. Apprehensive persons may also show such other indications of conflict as excessive giggling or laughing, sweating, and trembling, all of which are indicative of other deep-seated tensions and fears; weeping and crying are indicative of profound anxiety. Induction should not be continued in such emotionally disturbed persons because chagrin, a sense of failure, and other depressive reactions can readily be produced, especially in those with prepsychotic personalities. Unless the operator is experienced, he should terminate the induction. Although induction of hypnosis depends on the strength of the interpersonal relationship, it is an intensely intrapersonal problem for the subject.

The deep or somnambulistic hypnotic state is readily recognized; it is characterized by immobility of the facial features; staring eyes; loss of startle reflex; slow, slurring speech; catalepsy of large muscle groups; economy of motion; and a time lag or gap between the giving of a suggestion and the response to it. A medium depth is indicated by limb catalepsy, ease of lid closure, inability to open the eyes after closure, trembling and twitching of eyelids, and a more moderate degree of neuromuscular relaxation. Since the perceptual fields are narrowed to all sensory input, intense absorption in physiological activities occurs.

The skillful operator closely observes his subject's responses in order to use every voluntary or involuntary manifestation to reinforce the subject's expectation and belief that hypnosis will occur. For instance, if the subject's eyelids tremble involuntarily during the initial phase of induction, the operator can remark, "The trembling of your lids is a good sign that you are becoming more and more relaxed." If the patient voluntarily swallows one can say, "You just swallowed, that's good; it shows you are relaxing." Such points should always be made on a logical basis and bear the stamp of validity to be accepted. Also, one must avoid giving the impression that each and every suggestion will be acted on. If necessary, whenever a suggestion is not followed, the experienced operator changes to another so that the patient is unaware that either he or the operator has temporarily failed.

I strongly emphasize that better results will be obtained if the sequence of the suggestions is not broken. Before inducing hypnosis, it is a good idea to tell the subject what you are going to do, what he is to expect, and what you expect of him. Let him understand that you do not really induce the hypnotic state, that he does, and that you are only acting as a guide. If he follows elementary instructions, he will follow others and enter deeper states of hypnosis at his own pace and desire. When possible, it is generally helpful to have a new patient observe an induction procedure in a well-conditioned subject—a few minutes of observation is worth hours of discussion. Through emotional identification with patients who successfully enter hypnosis, the subject now understands what to expect and this helps to overcome resistances.

Techniques for deepening the hypnotic state are achieved by establishing a definite goal for each step of the induction procedure. "As you raise your arm higher and higher, with every upward motion of your arm you will become more and more relaxed." Linking these suggestions with physiological processes is helpful. For example, "With each beat of your heart you will become more and more relaxed." Vogt's fractionation technique[3] is an excellent one for deepening hypnosis. In this technique the subject is dehypnotized and asked what sensations of relaxation or drowsiness he had. These are then "fed back" to the subject, with suggestions that he will become more and more relaxed with each opening and closure of eyes.

Autohypnosis is often called autoconditioning or autogenic training. It is best produced by a progressive relaxation technique, which can be taught while the subject is under hypnosis. The subject is given specific instructions for inducing self-hypnosis as well as for dehypnotization. This is "patient-centered hypnosis" and differs greatly from the outmoded and dramatic authoritarian methods of the 19th century.

Autohypnosis, together with production of glove anesthesia, is ideal for obstetric hypnoanesthesia.[4] The suggested "anesthesia" of the palms is transferred to the abdomen during labor to mitigate the pain of the uterine contractions. Autohypnosis and glove anesthesia are particularly valuable during group training sessions, in which the "emotional contagion," inherent competitiveness, identification with successful subjects who readily develop autohypnosis, and desire to please the therapist all facilitate hypnosis.

For surgery a rehearsal or "dry run" under hypnosis raises the pain threshold by teaching the subject to know what to expect. Such experiential conditioning under hypnosis automatically raises the pain threshold.[5] This method is called Schultz's autogenic training.[6] When terminating hypnosis in those who have entered either light, medium, or deep states, it is imperative to remove all suggestions except those that are to be used posthypnotically.

The dangers resulting from faulty techniques are minimal. In the trained physician's hands, there are really no dangers from the use of hypnosis per se, but harm may result from what is said to a hypnotized person or from failure to understand the responsible psychodynamics. The same dangers occur (when physicians untrained in psychiatry treat severely disturbed patients) at the nonhypnotic level. Janet once said that the only danger of hypnosis was that it was not dangerous enough. Nevertheless, hypnosis should be employed only by doctors for specific purposes in selected patients. Physicians should also realize their limitations and not exceed their psychotherapeutic orientation or ability.

Summary and Conclusions

Induction of hypnosis should not be attempted until all misconceptions have been removed and the patient is comfortable and free from distracting stimuli. Thereafter, a confident and positive approach by the therapist will enhance his prestige and eliminate the conscious and unconscious resistances of some patients. The therapist must be alert to those signs which indicate whether authoritarian or permissive procedures are necessary. Sometimes a combination must be used, since rapport fluctuates.

All induction techniques employ ideomotor and "ideosensory" activities which produce a favorable "mental set" or attitude based on belief, confidence, and expectation, catalyzed by the subject's imagination; hypnosis occurs as the result of this reaction. All hypnotic techniques should also limit sensory input and narrow conscious awareness to the suggestions of the therapist. These suggestions must be repetitive, stress key words, and be delivered in a monotonous manner. Hypnosis is cumulative, and once initial suggestions have been carried out further suggestions will alter sensory and motor capacities to produce appropriate responses. To obtain responses the therapist must be conversant with the types of personality of patients who will react to each technique. He must also employ a technique which uses the highest potential of his own personality. Autohypnosis, which enables the patient to induce and terminate the hypnotic state, increases motivation, and this "patient-oriented hypnosis" differs greatly from the dramatic methods of the 19th century wherein the therapist "played God." Deepening procedures make use of the patient's experiential background; Vogt's[3] fractionation technique and Schultz's[6] autogenic training are valuable adjuncts.

In surgery, autogenic training and rehearsal raise the pain threshold. The "dry run" removes fear and tension. Group hypnotherapy is always the preferred method because of "emotional contagion." Those who readily enter the hypnotic state stimulate those less suggestible to a cooperative attitude and identification. Equally important, the time factor is obviated by inducing the hypnotic state in many patients simultaneously. An electronic instrument, called the brain wave synchronizer, now aids the operator's verbalizations in these group sessions by inducing varying degrees of hypnosis, probably by photic "driving" of the alpha waves.

Hypnotic induction can be as readily learned as the technique for making an abdominal incision. The real problem is what to do with the "scalpel" after that. Induction is just the first step and is, in reality, produced by the subject as a result of the conviction that hypnosis will occur. Much clinical experience is needed to become proficient, and only through experience can the necessary confidence be gained.

9735 Wilshire Blvd., Beverly Hills, Calif.

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"HYPNOSIS," ANALGESIA, AND THE PLACEBO EFFECT

Theodore X. Barber, Ph.D., Cambridge, Mass.

Pain is a composite phenomenon, and not all aspects of pain are abolished by hypnosis. Subjects who report that they experience hypnotic analgesia or hypnotic hallucination are able to carry out a similar type of behavior without a hypnotic induction procedure. It has not been experimentally demonstrated that hypnotic procedures offer more satisfactory relief from pain than do placebos. The placebo effect has been reported to give satisfactory relief from severe postoperative wound pain in about 30% of patients; estimates as to the number of persons who manifest or experience such phenomena as hypnotically induced analgesia, age-regression, hallucination, and amnesia range from 5 to 25% of the population. Narcotics and hypnotic procedures do not necessarily affect the sensation of pain per se. By mitigating anxiety and inducing a bemused state they alleviate discomfort and appear to suppress the pain sensation.

Within recent years hypnotic procedures have proved successful in minimizing the pain associated with childbirth, spinal cord injuries, terminal cancer, fatal burns, mastoplasty, and thyroidectomy.[1] Although hypnotic techniques are gradually finding a useful place in the anesthesiologist's armamentarium (especially in cases in which chemical analgesics are contraindicated), the means by which "mere words" spoken by one person to another are able to exert an analgesic effect has been left unexplained or has been discussed in terms of concepts which are themselves in need of explanation such as "the power of suggestion," "the unconscious," or "the trance state." Nevertheless, sufficient data have accumulated to delineate two factors which are responsible for the effectiveness of hypnotic methods in minimizing pain. One of these factors is similar to a placebo effect; the other resembles the mode of action of morphine. Before analyzing these factors, however, a brief discussion is necessary to clarify the concept of hypnotic "analgesia."

The Semantics of Hypnotic "Analgesia"

The term "pain" carries a number of connotations which require careful differentiation. The normal response to nociceptive stimulation includes at least three interrelated components: (1) the awareness of pain as a sensation, (2) discomfort or suffering, and (3) one or more systemic physiological alterations, such as an increase or decrease in blood pressure.[1b] With selected patients, hypnotic procedures can minimize discomfort and suffering and can minimize the physiological alterations which normally follow nociceptive stimulation, without necessarily affecting pain as a sensation. Dorcus and Kirkner,[2] for example, reported that hypnotic procedures alleviate suffering in patients with spinal cord injury not by suppressing "the primary pain-arousing mechanism" but by minimizing "factors that tend

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From the Department of Social Relations, Harvard University. Dr. Barber is now Research Associate at the Worcester Foundation for Experimental Biology and Medfield (Mass.) State Hospital.

Read in the Symposium on Hypnosis before the Joint Meeting of the Section on Anesthesiology and the Section on Nervous and Mental Diseases at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

to focus the individual's attention on the pain." My recent experiments and earlier experiments by others [1b] have demonstrated that, when the noxious stimuli are not too severe, some good hypnotic subjects do not show discomfort (by wincing, withdrawal, tremor, or restlessness) and do not show significant alterations in blood pressure, pulse rate, or respiration; however, careful questioning of these subjects reveals that the pain sensation is actually present but appears to be minimized or eliminated because the subjects are able to stop attending to, to concentrate away from, and to inhibit all thoughts about the noxious stimulation and the concomitant painful sensation.

The Good Hypnotic Subject

Although the amount of chemical anesthetic administered can be significantly reduced with most surgical patients by the adjunctive use of hypnotic procedures, persons who are able to undergo major or minor surgery with hypnotic procedures alone are a minority of the population, at least in Western nations. In the experimental laboratory, I found that hypnotic suggestions are effective in minimizing the discomfort associated with such noxious stimulation as Lewis' muscle ischemia tests [2a] in about 15% of a sample of the student population.[1b] Along similar lines, Winkelstein [3] reported that when hypnotic procedures are used without other analgesic agents 7% of 200 obstetric patients were able to give birth without noticeable discomfort or suffering. Other estimates as to the relative number of "somnambulists," i. e., persons who are able to experience such phenomena as hypnotically induced analgesia, age-regression, hallucination, and amnesia, range from 5 to 25% of the population.[4]

These persons possess distinctive characteristics and abilities. Young [5] noted that all of his good hypnotic subjects showed one or more of the following characteristics long before they were ever "hypnotized": "deep abstraction, reverie amounting almost to ecstasy, putting oneself to sleep at will, actually hypnotizing one's self." Similarly, in a series of investigations [6] I found that subjects who are able to experience such phenomena as hypnotic analgesia or hypnotic hallucination are also able to carry out a similar type of behavior without a hypnotic induction procedure. For example, these subjects typically report that they do not require a local anesthetic for dental work; prior to participating in hypnotic experiments, they had discovered that by thinking about something pleasant and inhibiting all thoughts concerning the dental situation they could undergo various dental procedures without discomfort.[6b] Apparently these persons are able to carry out the essential behavior involved in "hypnosis"—are able to become relatively inattentive and unresponsive to selected stimuli—with or without a formal hypnotic procedure.

However, to undergo major surgery or to be relieved of severe pain by hypnotic methods, the patient must also believe that "hypnosis" can relieve his pain and he must be set to accept his physician-hypnotist's words as valid descriptions of reality. Kroger [7] concluded from extensive clinical experience with hypnotic techniques that "when one wishes to perform major surgery under hypnoanesthesia . . . it is very important to get the patient to believe in the actuality of the trance state." Somewhat along similar lines, Leuba [8] concluded from his experimental work that "there must be a concentration on the ideas presented by the hypnotist and with a minimum of counter or critical thoughts; and a belief that what the hypnotist says will happen, can actually happen, and will happen. In other words there must be a set or attitude to accept the hypnotist's statements completely and uncritically." Recent experiments [9] indicate that these propositions are valid: "Somnambulistic" subjects do not carry out the more difficult hypnotic behaviors (such as hypnotic deafness or blindness, negative hallucinations, or analgesia to severe nociceptive stimuli) when the hypnotist simply gives them the appropriate suggestions. Something more is required: The hypnotist must manipulate his words and the situation in such a way as to lead the subject to believe that the suggestions are literally true statements. Clinical reports emphasize an additional factor which is closely related to this: The patient must have confidence in his physician-hypnotist. After use of hypnotic methods with 200 consecutive obstetric patients, Winkelstein [3] concluded that "the mental attitude of the patient, the patient-obstetrician rapport, and the confidence of the patient in the procedure as well as in the accoucheur, seemed to be as important factors as was the hypnosuggestion itself." Butler [4a] also noted that a close interpersonal relationship between physician and patient is necessary in treating the patient suffering from terminal cancer by hypnotic methods. He reported that when hypnotic procedures were abruptly terminated the patients all showed a dramatic return of the original suffering; however, when hypnotic methods were discontinued but the patients received the same amount of personal attention from the physician, discomfort and suffering were minimized for a few days to the same extent as during the hypnotic sessions. The author emphasized that when the physician uses hypnotic techniques he "gives of himself to the patients. Even an hour's treatment with a very sick patient can produce an appreciable tiring of the hypnologist, and, as the sympathetic bond between the two grows stronger, the hypnologist may even 'feel' the symptoms he is trying to eradicate from the patient."

In brief, hypnotically induced analgesia appears to involve two essential factors: 1. The patient must have confidence in his physician and believe that hypnotic procedures can relieve his pain. 2. The patient must become inattentive to, not thinking about, and unresponsive to the nociceptive stimulation. To the extent that the first factor is operative, hypnotic analgesia resembles a placebo effect. To the extent that the second factor is operative, hypnotic analgesia resembles the relief of suffering achieved by administration of morphine and other opiates.

Hypnotic Analgesia as a Placebo Effect

In extensive studies of severe postoperative wound pain, Beecher[10] found that about 30% of patients received satisfactory relief from a placebo. (The term "satisfactory relief" refers to the patient's judgment that he has received "50% or more relief of pain at 45 and 90 minutes after the administration of the agent.") Others have carried out similar studies and have confirmed these findings. Although hypnotic procedures may offer a more satisfactory relief than placebos, this has not been experimentally demonstrated and requires further investigation.

How does a placebo minimize the suffering associated with postoperative wounds or other pain syndromes? As a first approximation to an answer, it is difficult to disagree with Wolf's[11] conclusion that "'placebo' actions depend for their force on the conviction of the patient that this or that effect would result. . . . The fact that 'placebo effects' occur depends, of course, on the generalization established repeatedly by numerous workers that the mechanisms of the human body are capable of reacting not only to direct physical and chemical stimulation but also to symbolic stimuli, words and events which have somehow acquired special meaning for the individual."

In general, studies of the placebo effect suggest that the placebo reactor is responding to a "drug" which he believes has curative properties.[1b] This belief is a function of many factors: what the patient is specifically told about the "drug," the patient's previous experience with pain and with drugs, and his previous experience with the physician, the nurses, and the other hospital personnel. Similarly, hypnotic analgesia is partly a function of the patient's conviction that the physician-hypnotist will relieve his pain, which in turn is a function of his previous experience with pain, with his physician, and with hypnotic procedures.

Hypnotic Analgesia and the Effect of Morphine

It has generally been assumed that hypnotic analgesia has little, if anything, in common with the relief of pain effected by administration of morphine. However, a careful scrutiny of the evidence suggests that these seemingly diverse analgesic agents actually possess common characteristics: in both, pain as a sensation is not necessarily altered; in both, discomfort and suffering are minimized or eliminated; in both, the relief of suffering appears to be secondary to an alteration in the patient's concern with, attention to, or anxiety about the nociceptive stimulation. Wolff and coworkers[12] concluded from a series of investigations that after morphine administration "the pain sensation is perceived and is recognized as pain with no difficulties." More recent clinical and experimental evidence indicating that morphine and other narcotics can relieve discomfort and suffering without necessarily elevating the pain threshold or altering the sensation of pain has been summarized by Beecher[10] and myself.[1b]

The relief of discomfort and suffering appears to be one component of a more generalized effect of morphine which has been conceptualized as "freedom from anxiety," "contentment," and "a bemused state." Beecher[10] wrote, after extensive clinical and experimental experience with morphine and other analgesics, that "the narcotics really alter pain perception very little but do produce a bemused state, comparable to distraction, which they [the patients] can be 'alerted out of' and will then report on the little altered pain perception." Along similar lines, Hill and co-workers[13] concluded from a series of experiments that the relief of suffering effected by morphine administration may be secondary to a more general effect (which they term the relief of anxiety or fear of pain) and that morphine may be effective as an analgesic agent only when anxiety is present.

In brief, narcotics and hypnotic procedures do not necessarily affect the sensation of pain per se; however, by mitigating anxiety and by inducing contentment and "a bemused state," discomfort and suffering are alleviated and the pain sensation may appear to be suppressed.

Summary and Conclusions

There is no need for such concepts as "trance," "suggestibility," or "the unconscious" to understand the relief of discomfort and suffering produced by hypnotic methods. To understand hypnotic analgesia the emphasis should be placed on the characteristics of those relatively few persons who are able to experience this phenomenon. As a result of previous life experience, these persons are able quickly and easily to become relatively inattentive to, not thinking about, and unresponsive to selected stimuli. Given this type of person, and given a belief on his part that his physician-hypnotist will relieve his pain, discomfort and suffering are minimized by two interrelated processes which are also effective when administration of placebos and morphine relieve a pain syndrome. First of all, suffering is minimized because a placebo effect is operating; that is, the patient believes that pain will be relieved. A second factor is similar to the effect of morphine; morphine administration and hypnotic procedures alleviate a pain syndrome primarily by bringing about contentment, freedom from anxiety, and "a bemused state comparable to distraction," without necessarily altering the intensity of the painful sensation or elevating the pain threshold.

49 Ellery St. (38).

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HYPNOSIS—APPLICATIONS AND MISAPPLICATIONS

Harold Rosen, M.D., Ph.D., Baltimore

Hypnotic techniques can be readily taught. The only apparatus needed is the vocal apparatus of the physician hypnotizing the patient. But theoretically unsound and mutually inconsistent statements are made in this field, particularly in promotional material for fixation objects and hotel-room courses. Cases here described show that neither diagnostic uncovering techniques nor supposedly therapeutic chronological regression with abreaction is safe in the hands of persons ignorant of psychodynamics. Failures are as melodramatic as successes. No one should ever treat patients on hypnotic levels for therapeutic goals or with techniques beyond the range of his usual professional competence with unhypnotized patients. Used with due caution, however, hypnotic techniques have tremendous potentialities in medical practice.

Hypnosis will, in all probability, turn out to be a potent medical research tool.[1] It is even now of pronounced value in clinical practice. Hypnotic techniques, although they do not of themselves constitute treatment, may help to make it possible, in selected patients, to control physical and emotional pain, to allay anxiety and apprehension, and by mere verbal suggestion to cause even incapacitating symptoms to disappear.

About 25% of the general population—figures in the literature vary from 15 to 35%—may be hypnotized deeply enough, in a short enough period of time, for hypnotic induction techniques to be clinically usable by physicians. Patients can be hypnotized whether they are standing up, sitting on a chair, or lying in a hospital bed. They can be hypnotized whether they wish to be or not. They can be hypnotized without conscious awareness on their part that hypnotic induction is being attempted.

Chairman, Committee on Hypnosis, Council on Mental Health, American Medical Association.

Read in the Symposium on Hypnosis before the Joint Meeting of the Section on Anesthesiology and the Section on Nervous and Mental Diseases at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

They can be hypnotized by suggesting eyelid closure; yet even during the first induction process their eyelids may never be closed.

Techniques of Hypnosis

Most induction techniques make use of the voice. Physicians by training are accustomed to the use of drugs and as a result some colleagues feel more comfortable if intravenously given barbiturates, such as thiopental (Pentothal) or amobarbital (Amytal) sodium, or other chemotherapeutic agents are prescribed. For most patients, however, this is not necessary. Some colleagues use fixation objects and have patients focus on a spot on the wall or ceiling, on a finger, eye, or pen, or on a glittering object. These may cost a few cents or a few hundred dollars, depending on how elaborate they are and how much science fiction and science fantasy—in the form of theoretically unsound statements or misstatements about brain-wave tracings, extrasensory perception, or whatnot—are emphasized in the promotional material. Neither drugs nor machines, however, are needed. The spoken word is usually more than sufficient.

A large number of oral induction techniques have been described.[2] The classic ones—and it is these that are taught physicians—are characterized by monotonous suggestions that the patient feel relaxed, breathe deeply but comfortably, close his eyes, and feel sleepy or fall asleep. It may be added that he will—or will not—remember, forget, or misremember whatever he does, says, or feels while hypnotized. Posthypnotic suggestions can be given him. If analgesia or anesthesia is the desideratum, for obstetric or surgical purposes, he may be told that he feels nothing or, alternatively, that whatever it is that he does feel will not annoy, disturb, pain, or otherwise affect him. Dry runs—rehearsal deliveries or rehearsal operations—may also be carried out.

The only apparatus needed for this is the vocal apparatus of the physician hypnotizing the patient. As a result, hypnotic techniques can be readily taught. For most physicians 15 to 30 minutes' instruction is more than sufficient. It seems little short of magical that so much can be accomplished through techniques so readily mastered. But, unless the physician has had adequate training in psychodynamics, hypnosis may be extremely dangerous for his patient without his realizing it.[3]

Results are nevertheless startlingly melodramatic. So, incidentally, are failures. Some colleagues hypnotize patients for preoperative sedation, others to set fractures. The value of hypnosis in physical medicine during the rehabilitative process is self-evident. Most articles emphasize its value as an analgesic, anesthetic, or tranquilizer. Some urologists, without using the word "hypnosis," over a two-minute or three-minute period attempt to hypnotize patients for catheterization. If they succeed, the patient is much less uncomfortable than he otherwise might be; if it does not "take," only a few minutes has been lost; and the patient is catheterized in either case.

Indications and Contraindications

Patients can be hypnotized in medical practice for a number of other reasons as well. The patient who has had a heart attack, for instance, like the patient with peripheral vascular disease for whom surgery is recommended, may find it difficult or impossible to smoke less or to cease smoking. His tobacco intake may be blocked by posthypnotic suggestion. The patient with severe pruritus (from poison ivy, for example, or a trichomonal infection) may posthypnotically no longer be plagued by the itch. Obese patients may posthypnotically adhere to the optimal diets prescribed and lose weight without regaining it later on. Patients with neurotic or psychotic diseases may be hypnotized and cure of symptoms suggested.

However, the physician in general practice or in one of the specialties who hypnotizes patients when he believes it indicated always attempts to determine in advance[3A] whether or not the patient can comfortably—and in his own best medical interests—carry out the suggestions given him. He guards against adverse effects. If smoking cigarettes, for example, is the only means that a particular patient with cardiovascular disease has of relieving his tension, he will give him some other tension-relieving device before stopping his smoking. Otherwise, with no means of letting off steam, his blood pressure level may increase up to 50 points, and apparently innocuous posthypnotic suggestions to decrease or cease smoking may impose an additional strain on an already over-burdened cardiovascular system and be harmful instead of helpful.

The same statement can be made about patients hypnotized for other reasons.[4] One patient whose severe generalized pruritus was hypnotically "suggested away" was almost overwhelmed with sexual desire for the lover who had deserted her immediately after procuring her abortion; furthermore, she now felt an almost homicidal rage against him. With the relief of her physical itch she now emotionally "itched"—I know of no other way by which to characterize it—both to possess and to kill him. It therefore seemed advisable to relieve her dermatological pruritus not by hypnotizing it away but by treating some of the emotional tension-producing factors which underlay it. A patient with phantom-limb pain that was successfully suggested away while he was hypnotized[2a] had to be hospitalized psychiatrically because of an underlying schizoaffective psychosis that, a short time later, erupted into overt symptom formation. Hypnosis, even with magical pain relief, can be dangerous.[3]

Summary of Casts

It is easy enough to hypnotize, but it is of prime importance to know when not to. For this reason, whenever patients request hypnosis their motivation for this and their reasons for requesting it need evaluation. One patient, for instance, after having dental work done under hypnosis, on several occasions persuaded her dentist to hypnotize her so that she would cease smoking. His posthypnotic suggestions were ineffective. She ultimately but reluctantly accepted referral for psychiatric consultation to determine why, despite strong hypnotic suggestion, she was unable to cut down on her cigarette intake. It appeared that she was a lonely widow who hoped her dentist would fall in love with her. She smoked only a few cigarettes a day, but seized on this to make further appointments with him. It took a one-and-one-half-hour interviewing session, however, to elicit this. Needless to say, she was not hypnotized by the psychiatrist.

Neither was a patient who three or four years previously had had a radical mastectomy. A nodule had appeared on her sternum and was now under investigation. She asked to be hypnotized so she could forget—and forget completely—that she had ever had cancer. During the consultation session it became evident that she was a very depressed woman. In view of the fact that she had had a malignancy and that a recurrence was in the offing, this was understandable. However, a number of slips of the tongue showed that only religious scruples had kept her from killing herself. She wished to blot out not only memory of her past cancer, not only memory of part of her past life, but her whole life itself. It became obvious, from further slips of the tongue, that she was not aware of this on conscious levels. Hypnosis to her would have been tantamount to permission to commit suicide. This was not called to her attention, nor was her husband told of this. Hypnotic induction was not attempted. Instead, both she and her husband were seen—although separately—over a few interviewing sessions, in order to help each reach the point of requesting psychiatric hospitalization for the treatment of her underlying emotional problems, while the possibility of recurrence of her cancer was being further investigated. This apparently minor but actually major therapeutic goal was achieved. She remained in the psychiatric department of the hospital for several months. This was some years ago, and the patient is still alive and is well.

This patient in all probability was readily hypnotizable. It is highly probable that with strong hypnotic suggestion she could have become amnesic for her mastectomy and her cancer. Neither she nor her husband would have seen any correlation between what to them would have appeared a miraculous hypnotic cure and her later suicide. Despite the probability of her self-inflicted death, her husband would have remained grateful to the physician, if he had hypnotized her, for having helped her so much before the end.

Some colleagues may consider this an extreme example, but it illustrates the problem with the sharpness of caricature. It is of prime importance to know when not to hypnotize. There is no dearth of illustrative case material. For instance, a compulsive smoker in her 30's was given a posthypnotic suggestion to cease chain-smoking. The suggestion was effective. She was grateful to her hypnotist, felt that he had "cured" her of cigarette smoking, and did not correlate her present distaste for cigarettes with the compulsive overeating that soon took its place. By the time she had added 40 lb. (18.2 kg.) to her weight, she sought out a second hypnotist who "cured" her of her obesity. She then—but much later—gradually began drinking more and more, found herself too intoxicated one day to attend to routine social commitments, and requested a third hypnotist to "cure" her alcoholism. To her, her compulsive chain-smoking, overeating, and alcohol intake were three completely unrelated problems. She spoke about each of her previous hypnotists in glowing terms. Her descriptions reminded one of quack cancer-cure testimonials made by patients a few months before they are hospitalized *in extremis.*

I have seen a number of patients who have been hypnotized by not one but several colleagues and about whom the same comment can be made. This is especially characteristic of the obese patient who after five or six months finds it impossible to retain her weight loss but who nevertheless on a follow-up questionnaire gives her hypnotist to understand that obesity is no longer a problem. She does not, so she states, wish to hurt her physician's feelings.

Abuses of Hypnosis

This is not to decry the use of hypnosis. Ever since Mesmer physicians have been impressed by apparent cures attained through direct hypnotic suggestion—and then disappointed. Although more effective than suggestion on nonhypnotic levels, hypnosis frequently is not sufficient. Follow-up studies over a prolonged period of time are indicated. Long-term studies[5] do not confirm short-term hopes. For this reason, if for no other, courses now offered by lay or professional personnel to dentists and physicians stress not only suggestion but chronological or age regression and abreaction. These techniques have been emphasized and re-emphasized in lay periodicals and in technical journals, as have uncovering techniques.

These therefore require further discussion. I have already mentioned a patient with diabetic gangrene who after a leg amputation developed phantom-limb pain that persisted after a neuronectomy, as a result of which narcotics ultimately were prescribed for him as needed. He was hypnotized and his pain was readily suggested away. It was not known if this was safe, since pain that persists for emotional rather than physical reasons frequently either is a depressive equivalent or serves to help hold a depression on leash. On investigation it turned out that this patient "knew" that like his wife before him he already had metastases, would need multiple surgery, would learn that this nevertheless was too late, and would like his wife die a lingering, agonizing death. Psychiatric treatment, preferably on a hospitalized basis, was recommended but refused. As long as he could concentrate on the pain in his stump he could forget or escape preoccupation with his underlying fears. With the relief of the pain [2a] he saw no reason for further treatment. Psychiatric hospitalization as a result ultimately became mandatory. It might have been better if while he had still had his pain a psychiatric treatment relationship had been established. This was attempted with a patient, reported by Joseph and co-workers,[3a] whose pruritus of six months' duration was hypnotically relieved and who then developed a psychotic depression.

Two other hypnotic techniques, time regression and abreaction, are usually taught physicians. Patients once hypnotized can be ordered to pass back through time to the event or events that, it is alleged, must be considered the cause of their asthma, epilepsy, torticollis, diabetes, headache, insomnia, back pain, alcoholism, or homosexuality. They are then told to relive (i.e., abreact) this emotionally traumatic event and be cured.

With traumatic neuroses this may be indicated, but it may not. Merely regressing a patient to a specific incident may or may not be helpful. With a Kentucky coal miner who had been caught in a cave-in, it was. His severe choking and gasping spells which on two occasions had been misdiagnosed as asthma disappeared, as did his almost constant feeling of being suffocated. An adolescent with a wry neck, however, when regressed in this way, relived a sexually traumatic episode and his torticollis immediately disappeared. The surgery for which he had been tentatively hospitalized became unnecessary; however, he then became an exhibitionistic practicing homosexual. He would perhaps have been better off if his wry neck had not been "cured" in this way.

The self-styled hypnoanalyst without years of psychiatric (and analytic) training can be a dangerous person to have around, and so can the self-appointed teacher of the subject. A patient with severe back pain persisting after a laminectomy was abreacted by one of these. His pain disappeared posthypnotically, and the following week he committed suicide by jumping out of an upper-story window. If his back pain was organically based, this abreaction was not indicated. If it were thought that emotional factors were partially or completely responsible for it, then psychiatric consultation or hospitalization should have been requested. Pain, it should be emphasized, if emotionally based or if continued for emotional reasons, frequently masks severe and even suicidal depressions or serves as their equivalent. No patient with back pain, phantom-limb pain, intra-abdominal or intracranial pain, or even atypical trifacial neuralgia pain should ever be approached on hypnotic levels, by dynamically untrained personnel, with techniques more potent than those of mere verbal suggestion. No one, in fact, should ever treat patients on hypnotic levels with techniques beyond the range of his usual professional competence with unhypnotized patients.[6]

The literature is filled with direct misstatements of fact in this area. One frequently reads that psychotic patients cannot be hypnotized or can be hypnotized only with such difficulty as to make their hypnosis clinically impractical or impossible. Persons who make such statements either have no first-hand knowledge of the subject or are unable to recognize psychosis when they see it. A number of cases [3] have been reported in the literature and additional case reports are now in publication.

The problem is a pronounced one, since large numbers of patients show somatic symptoms rather than disturbed behavior. Their diagnosis is what, for want of a better term, has been labeled a compensated (psychoneurotic, dissimulated, borderline, or masked) psychosis. Suggesting away a single symptom may be dangerous unless such patients have several symptoms to fall back on. A single symptom can often be the last defense against decompensation.[7]

It may perhaps be for this reason that, in so many of the two-day and three-day courses advertised for physicians and dentists, hypnosis has been characterized as a powerful uncovering technique. Articles are appearing frequently in current medical literature advocating its use to pin-point the cause of various hysterical symptoms and so-called psychosomatic diseases. This can be dangerous. A woman with ulcerative colitis, for instance, when hypnotized and regressed, acted out an incestuous episode which took place when she was 5 or 6 years of age with an older brother. One month after his funeral her ulcerative colitis became symptomatically severe enough to necessitate her first hospitalization. If she had been allowed to remember this material on nonhypnotic levels, she might in all probability have gone into an overt depressive or paranoid psychosis. It is not what is uncovered or learned that is of importance, but how this can be used to help the patient. And this would have been harmful, not helpful, to her at the time.

Uncovering techniques, incidentally, are not often used even in internal medicine. If a patient has a heart murmur or a coronary condition, no one would suggest intrathoracic surgery so that the cardiologist could see, and therefore understand, the exact nature and full extent of the patient's cardiac disease. No well-trained psychiatrist would do emotional surgery merely to lay bare emotional disease, since this would be equally dangerous to the patient and of no value to him. It is exceedingly melodramatic for the hypnotist who does this, but it should be discouraged.

Nevertheless, chronological regression with abreaction is advocated constantly. A recent book on hypnosis in dentistry is filled with example after example of the use—to me it seems the misuse—of these two techniques in dental practice. Announcements of two-day and three-day courses on hypnosis for physicians, of the type now flooding the country, invariably list these as among the subjects taught. Their instructing staffs, both medical and lay, seem to feel that with this they are teaching psychodynamics; they do not realize that only hypnotic techniques are being taught.

During the past several years a number of persons have started calling themselves "hypnotists to the medical profession." Some of these are now importuning hospitals for operating-room and delivery-room privileges, for the purpose of hypnotizing patients for surgery or childbirth.[8] They have no medical competence and little or no knowledge of the complex phenomena involved, know nothing about the motivational bases of human behavior, and in my opinion should be denied such privileges. As the A. M. A. "Report on Medical Use of Hypnosis" states, "The utilization of hypnotic techniques for therapeutic purposes should be restricted to individuals who are qualified by background and training to fulfill all the necessary criteria that are required for a full diagnosis of the illness which is to be treated."[6] These so-called hypnotists to the medical profession do not have this training, nor do those persons with little or no knowledge of psychodynamics who wander from city to city, sending announcements to all physicians and dentists in the telephone book, and advertising one-day, two-day, or three-day hotel room courses which stress induction and potentially dangerous uncovering techniques.[7]

Summary

Hypnotic techniques have tremendous potentialities in medical practice. They can be used for sedative, analgesic, or anesthetic purposes; to make symptoms disappear; for tranquilization; or as an adjunctive technique when patients with neurotic or psychotic disease are under treatment. Before patients are hypnotized, their physical and emotional status and their motivation for seeking hypnosis need evaluation. For this, training in psychodynamics (the motivational bases of human behavior) is essential.

Results achieved depend to a large extent on the relationship between physician, or hypnotist, and patient, or subject. If such relationships are not understood, harm can result. Indiscriminate hypnosis may be dangerous. When physicians, whether in general practice or in the various specialties, use hypnotic techniques, it should be for purposes of and with techniques related to the particular specialties and within, not beyond, the range of usual professional competence when patients are seen and treated on nonhypnotic levels. We are otherwise playing with dynamite.

1101 Calvert St. (2).

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BRONCHIOLITIS IN INFANTS

PROBLEM IN PRACTICE

James L. Dennis, M.D., W. Martin Palmer, M.D.
and
Robert W. Cleveland, M.D., Oakland, Calif.

Bronchiolitis is a term applied to any inflammatory disease which afflicts the bronchioles. When it occurs in infants of less than 1½ years of age, it produces a distinct syndrome. The hospital charts of 1,200 children with bronchiolitis were reviewed for data on the salient features of the syndrome. It usually started with a mild upper respiratory infection. In the acute phase, obstruction of the bronchioles developed due to inflammatory edema and exudation; the resultant manifestations in the patient were dyspnea, cough, expiratory wheezing, and emphysema. This syndrome resembles that observed in the child with asthma who has an upper respiratory infection, but it differs in prognosis and in the fact that the infant with bronchiolitis does not improve after administration of epinephrine. The treatment is generally supportive but must be varied for the individual patient; it is directed toward the prevention of fatal complications, the most common being secondary bacterial bronchopneumonia and right heart failure.

The word bronchiolitis is a general term applicable to any inflammation of the bronchioles. Although many different viral, bacterial, or allergenic agents might initiate such a process in any person at any age, the clinical picture of infectious bronchiolitis in infants constitutes a distinct pediatric syndrome.

During the 10-year period 1947-1957, bronchiolitis was exceeded only by diarrhea as a cause for admission to the infant wards of the Children's Hospital of the East Bay. More than 1,200 of these cases have been reviewed to provide the basis for this report. In 483 (40%) the baby had been considered to be in critical condition at some time during the hospital stay, and in 2% the baby did not survive.

In spite of the common occurrence, serious morbidity, and definite mortality from this syndrome, many physicians appear to be unfamiliar with infectious bronchiolitis in infants. Almost invariably, the allergist, the internist, and the generalist referred to bronchiolitis as "asthma." Fifty-one per cent of the pediatricians used bronchiolitis as a diagnostic term when the patient was admitted; the rest used various designations, including asthma, asthmatic bronchitis, capillary bronchitis, interstitial pneumonia, pneumonitis, and acute emphysema. Apparently there is a problem in meaning as well as in understanding.

Clinical Features

The clinical course of infectious bronchiolitis in the infant is fairly constant. A "cold" or a simple respiratory infection of several days' duration precedes an acute onset of dyspnea, cough, expiratory wheezing, and emphysema that often becomes progressively worse in spite of treatment. This alarming period of respiratory distress persists for an average of two to three days and is followed by another two or three days of clearing by lysis. In 70% of patients the temperatures remained under 101 F (38.3 C), but they ranged between 98 and 105 F (36.7 and 40.6 C).

Subtle features related to the anatomic and physiological peculiarities of the infant are important to an understanding of the syndrome in this age group. It is known that with inspiration the bronchioles increase in diameter and that on expiration they diminish in size. For this reason, the presence of bronchospasm, hyperemia, edema, cellular debris, or mucopurulent exudate will result in varying degrees of obstruction that become apparent only during expiration. As air is trapped, emphysema develops. Eventually the diaphragm is compressed and flattened so that vertical excursion is no longer possible. However, with each inspiration, the powerful diaphragmatic muscle continues to contract, exerting a forceful pull on its attachments to the chest wall. The rigid, bony cage of the older child and adult can resist this force; the soft, elastic thorax of the baby can only collapse inward. This produces a unique paradox, characterized by prominent inspiratory retraction of the lower chest and sternum in a condition that is primarily a problem of expiratory obstruction, a distinctive set of circumstances found at no other time in life. In our series 98% of the babies who presented this picture were under 18 months of age, and 92% were under 12 months of age.

Causal Factors.—Although many authorities [1] have demonstrated the role of viruses and others [2] have isolated common bacterial pathogens from

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From the Children's Hospital of the East Bay. Dr. Cleveland is now at 5479 Abbeyfield St., Long Beach 15, Calif.

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babies with bronchiolitis, many physicians persistently regard and treat this disorder as a manifestation of allergy.[3]

The possibility that hypersensitivity is a factor in bronchiolitis cannot be ignored. We have explored several areas that might elucidate this problem. In follow-up studies of 400 children who had been hospitalized for bronchiolitis as infants, only 33 (8.8%) gave a history of more than one episode of bronchiolitis, and only 12 of the children had definitely developed asthma. In contrast, a retrospective study of 100 asthmatic children revealed that more than half (54%) of them had repeated episodes of "bronchiolitis" during infancy.

Because of the almost specific effects of epinephrine in patients with asthma, a survey of the response to epinephrine was accomplished. Of the 1,200 hospitalized patients reviewed, 780 babies had been given epinephrine as a part of the initial medication. In only 39 (5%) was there an unqualified sustained clinical response. The seriously ill infant with infectious bronchiolitis is suffering from mechanical obstruction of the tiny bronchioles by inflammatory edema and exudate. In asthma, and possibly in the early stages of bronchiolitis, the major component of the obstructive force is bronchospasm; hence, symptoms are often—and sometimes dramatically—relieved by administration of epinephrine. This suggests that epinephrine administration might provide a diagnostic and prognostic test in an infant with symptoms of bronchiolitis.

The possible relationship of nasal eosinophilia and allergic disease has been considered. Nasal smears were obtained from 25 infants with bronchiolitis (with use of the technique described by Hansel[3a]). No consistent pattern was discernible, and the incidence of increased nasal eosinophilia was no higher in the babies who had bronchiolitis than in a control group of babies.

For the past two years we have obtained total blood eosinophil counts from babies with bronchiolitis. Normally, the total circulating eosinophil count in an infant will range between 100 to 300 per cubic millimeter. A stimulation of the "alarm reaction" by the stress of an infection can be expected to produce a drop in this number to between 0 and 25. Thus, a relatively high total circulating eosinophil count might indicate inadequate adrenal response to the stress of infection or the presence of a definite allergy. Eosinophil counts were obtained from 187 babies with bronchiolitis, and in only 6 (3%) was there a total count above 50. In 9 babies (4.8%) the eosinophil counts ranged between 25 and 50, and in 172 (91.5%) the count was between 0 and 25. One must concede the limitations of this simple, inexpensive laboratory procedure, but it may have practical application as a guide for the selective use of adrenal corticosteroids in the treatment of bronchiolitis.

Turning our interest to the infectious aspect of bronchiolitis, we conducted a survey of the families of 256 babies with bronchiolitis. In 93% of the cases respiratory infection had been present in other members of the family concurrent with the baby's illness. Like "croup," bronchiolitis occurred in small, epidemic periods; when one patient was admitted to the hospital it was usually the signal for several more to follow. The "cold" preceding the onset of symptoms, the presence of respiratory infection in family contacts, and the epidemic features of bronchiolitis appear to support the etiological role of the virus. Bacterial infection with Hemophilus influenzae, staphylococci, and pneumococci probably, in most instances, represent complicating secondary involvement.

Treatment

Few conditions in pediatrics evoke the multitude of routine orders that are provided the baby with bronchiolitis. The fact that the average length of the hospital stay for a patient with bronchiolitis (six days) was not altered during the 10-year period reviewed appears to be the most appropriate comment that can be made. The spectrum of therapy is outlined in the table. It is easier to discuss the inadequacies of therapy than it is to isolate factors that are of unquestioned value. The following program has, in our experience, been a positive and efficacious one.

General Supportive Measures.—Parenterally given fluids are prescribed when a baby is too ill to eat or drink or when there is dehydration. Fluids are given in sufficient quantity to cover insensible water losses and urine output. Electrolytes are added as indicated, and calories are provided by administration of glucose. Little attention has been accorded this aspect of therapy in infants with bronchiolitis, but the maintenance of adequate renal flow and glycogen stores is necessary to prevent metabolic acidosis from becoming superimposed on a respiratory acidosis.

Oxygen.—A 40% concentration of oxygen is maintained by continuous nebulization. The mist, or aerosol, provided by nebulization of distilled water (with or without wetting agents) creates a high-humidity atmosphere, minimizes insensible water loss, neutralizes the drying action of oxygen, and assists in the liquefaction of secretions.[4]

Antibiotics.—We do not advocate the routine use of antibiotics as prophylactic agents, but when a baby with bronchiolitis develops leukocytosis, high fever, and clinical signs of bacterial infection, we obtain appropriate cultures and initiate antibiotic therapy. Until cultures dictate otherwise, a program of chloramphenicol, 50 to 100 mg. per kilogram of body weight per day, and penicillin, 600,000 units per day, is preferred because of the high incidence of Hemophilus influenzae, staphylococcus, and pneumococcus infections in patients with the terminal bronchopneumonias of bronchiolitis. In our series the mortality rate dropped from 5% in 1947 to 2% in 1957. Although it was not possible to establish an unequivocal correlation with any particular mode of therapy, the most important single factor appears to have been the control of fatal, secondary bronchopneumonias by the use of antibiotics.

Spectrum of Therapy for Bronchiolitis

1. Oxygen
   40% in continuous nebulization
2. Liquefying Agents
   a. Aerosol mists (wetting agents, e. g., sterile aqueous solution of Superinone [oxyethylated tertiary octylphenolformaldehyde polymer] in combination with glycerine and sodium bicarbonate [Alevaire] and glycerine and propylene glycol, 2.5% each, in distilled water [Mistogen])
   b. Enzymes (e.g., proteolytic trypsin, desoxyribonuclease, crystalline trypsin [Parenzymel])
   c. Expectorant drugs (e. g., iodides, ipecac)
3. Bronchodilating Agents
   a. Epinephrine, ephedrine, phenylephrine (Neo-Synephrine) hydrochloride (prescribed to relax bronchospasm; not too effective in bronchiolitis and may have undesirable side-effects)
   b. Isoproterenol (Isuprel) hydrochloride; 1:200 dilution is effective by mouth or in an aerosol; may be used in patients with heart failure
   c. Xanthines: aminophylline, most widely used. Smooth muscle relaxant vasodilator and expectorant effects not prominently helpful to infants with bronchiolitis. Dose as rectal suppository should not exceed 7 mg./kg. of body weight (see text)
4. Mucosal Shrinking Agents
   a. Ephedrine or phenylephrine in mists or nose drops, as 0.05 to 0.1% solutions. Should be used for short intervals because of hypertensive and central nervous system effects. Ephedrine augments toxic effects of aminophylline
5. Antibiotics
   Prevention of fatal secondary bacterial infection is a goal in treatment. Hemophilus influenzae, staphylococci, and pneumococci are common pathogens; hence chloramphenicol, 50 mg./kg., and penicillin, 500,000 units, daily
6. Digitalis
   Digoxin, .075 mg./kg.
   Digitoxin, .035 mg./kg (see discussion in text)
7. Intermittent Positive-Pressure Breathing
   Controlled oxygen delivery with positive pressures, said directly to dilate bronchi, stimulate cough, wash out CO_2. Requires specialized equipment and experienced operators
8. Corticosteroid Hormones
   Indications not established (see text for discussion)
9. General Supportive Meaures
   Fluids, electrolytes, calories; by parenteral route if baby is not eating and drinking

Digitalization.—The occurrence of right heart failure in babies with severe bronchiolitis has not been widely recognized.[5] Admittedly, heart failure is difficult to evaluate when dyspnea, tachycardia, and a depressed liver constitute part of the primary illness; but if there is a persistently critical condition, tachycardia of 180 or more per minute, gallop rhythm, and a sudden, unexplained increase in the size of the liver, we digitalize. Digoxin, 0.075 mg. per kilogram of body weight, has been most efficacious in reversing these signs.

Other Modalities.—The preceding measures are of unquestioned value. Two other therapeutic measures that we are currently evaluating in controlled studies are intermittent positive-pressure breathing and use of adrenal cortical steroids.

Intermittent Positive-Pressure Breathing: Intermittent positive-pressure breathing requires specialized equipment for use in infants and the presence of a skilled operator. On occasion, this technique has appeared to be useful in correcting acute carbon dioxide retention, with respiratory acidosis. A few bursts of oxygen with controlled pressure stimulates cough and bronchial dilation and appears to improve ventilation.

Adrenal Cortical Hormones: Although we have consistently opposed the use of adrenal cortical hormones in patients with bronchiolitis, we have been impressed by some recent experiences with a new intravenous preparation, methylprednisolone sodium succinate (Solu-Medrol). In a pilot study this has been dramatically effective and without undesirable side-effects. However, the final answer must await prolonged and intensive observation under controlled conditions.

The fact that one physician out of three prescribes adrenal cortical hormones in the treatment of bronchiolitis deserves consideration. There is no evidence that adrenal insufficiency is a primary factor in patients with bronchiolitis; corticosteroids are not bronchodilating agents; and most authorities agree, in principle at least, that corticosteroids should not be used in patients with unknown infections.

Proponents may argue that adrenal cortical hormones are the most effective anti-inflammatory agents at our disposal and that, in spite of theoretical objections, they may be used with relative safety in short-term, self-limited infections, particularly when their use is covered by appropriate antibiotics.

In the cases reviewed, various corticosteroids appeared to modify the early critical phase of bronchiolitis in only an occasional instance. But this was difficult to evaluate, since similar responses were sometimes seen in babies who had not received hormones. Of interest is the fact that the average hospital stay for the babies who had received steroids was six days, identical to that for infants who did not receive steroids.

Until indications have been better established, we believe that corticosteroids should be reserved for use in certain rare occasions only; namely, those desperate situations in which all other therapy has been futile; when there is present an identified bacterial infection amenable to an available antibiotic; and for those instances in which the total circulating eosinophil count is elevated.

Summary

The cardinal manifestation of bronchiolitis from any cause is expiratory wheezing; therefore, "All that wheezes is not asthma." Bronchiolitis in infants is nearly always the result of an infection, usually a virus, producing a typical age-group response to a simple respiratory infection that only mildly inconveniences the adult. Asthma can induce a similar picture, but its symptoms are often alleviated by epinephrine, its typical course is short, and repeated attacks are common. The infant with a single episode of infectious bronchiolitis is quite unlikely to develop asthma in later life, but most asthmatic children have been subject to attacks of bronchiolitis as infants. The tendency to overtreat infants with bronchiolitis probably reflects the lack of specificity of any mode of therapy. Although many new therapeutic agents have been prescribed, the average length of the hospital stay has not been altered in the 10-year period 1947-1957. Aminophylline poisoning, due to excessive dosage in rectal suppositories, has become one of the most frequent complications of therapy. For these reasons, treatment should be directed toward general supportive measures and the prevention of potentially fatal complications, the most common being bronchopneumonia, right heart failure, fluid and electrolyte imbalance, and iatrogenic drug intoxication.

The methylprednisolone used in this study was supplied for investigative purposes as Solu-Medrol by the Upjohn *Company, Kalamazoo, Mich.*

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EXTRADURAL OSSEOUS LESIONS SIMULATING THE DISK SYNDROME

Harry R. Walker, M.D., Oakland, Calif.

Seven patients with complaints and physical findings suggesting a diagnosis of herniated intervertebral cartilage (disk syndrome) were found, on more thorough study, to have neoplastic disease of the bone. Roentgenographic examinations were done to show the vertebrae in better detail than before and to survey bones other than the vertebrae. In three patients the neoplastic process involved lumbar or sacral vertebrae, but in three others it involved the pelvis and in the seventh it involved the femur. In cases of supposed disk syndrome a thorough study of the rest of the skeleton should be done before elective surgery is attempted on the vertebral column.

During the last 20 years I have been confronted with many problems in orthopedic surgery but none so complex as the diagnosis and treatment of lesions of the lower part of the back, namely, the lumbosacral spine and pelvis. This paper pertains to one aspect of the problem of the low back, that of osseous lesions which simulate a common entity, the disk syndrome. I think all physicians, after 25 years of development, believe they can diagnose a herniated disk, particularly with the aid of a neurologist and with use of myelograms. However, these lesions I am about to describe frequently have not been looked for or have been neglected or overlooked by the neurosurgeon, the orthopedist, or the radiologist. While some of them are not common, they are more common than one anticipates and should be considered in most diagnoses.

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I have encountered seven cases, which will illustrate some of the things that can be misconstrued or misdiagnosed. They are, in my mind, major orthopedic problems.

Report of Cases

Case 1.—A 20-year-old man was inducted in the armed services one year prior to his admission to the naval hospital in Oakland. On admission he was in obvious distress and was reluctant to move because of pain in his back which radiated down into his right leg. He had had an insidious onset of pain in the lower part of his back after gunner exercise, in which he was required to lift heavy shell casings. He was put to bed for two weeks and was then admitted to a base hospital with a diagnosis of a herniated disk. Then he was returned to the mainland for further care. On admission he was uncomfortable, with pain in the back which extended down the right leg. He was found to have marked limitation of motion and muscle spasm in the lumbosacral area, with tenderness over the sacroiliac joint and along the course of the sciatic nerve. He had a strongly positive straight-leg-raising test on the right, with some hyperesthesia over the lateral aspect of the right calf. All reflexes were present and unimpaired. X-rays taken at a base hospital accompanied the patient and results were essentially negative when reviewed. His laboratory findings, consisting of results of blood studies and urinalyses, were within normal limits. He had a slight elevation of temperature for two days and an increase in the white blood cell count of about 1,000 per cubic millimeter, with some elevation of the sedimentation rate. His symptoms increased, in spite of traction, while he was in the hospital. On the third day he was given an enema, and roentgenograms were made of the lumbosacral spine and pelvis which showed a lesion that was suggestive of malignancy in the right sacroiliac joint. A biopsy specimen revealed Ewing's sarcoma. No other surgery was contemplated, and he was treated by radiation therapy.

Case 2.—A man about 69 years of age had a history of an insidious onset of low back pain, which radiated down the posterior aspect of the thigh, about six years ago. He was first examined by a general practitioner in a western city and then referred to a neurosurgeon who performed a laminectomy on the right side between L-4 and L-5, without relief of his symptoms. Two years later he had another laminectomy, and this too proved futile. The interspace between L-4 and L-5 was explored. Degenerated disk material was excised and removed. The patient felt better for a while; then his former symptoms recurred, and he developed a slight limp on the right side. Eighteen months later he had another exploratory laminectomy with a spinal fusion between L-4 and L-5. As soon as he had recovered from this operation his former symptoms recurred, and one year later he was referred to a large clinic in the middle west.

Physical examination revealed slight limitation of motion in the lumbosacral spine, multiple operative scars over the lower part of the back, atrophy of the right gluteus muscle, and tenderness over the lumbosacral spine, the sacroiliac joint, and the posterior aspect of the hip and down the course of the sciatic nerve to the knee. The results of his neurological examinations were negative, except for a diminished ankle jerk and positive straight-leg-raising test result. The hip joint functioned well. He had a full range of motion in all planes, and there was no weakness of any muscles other than those of the gluteal group. There was no measurable atrophy of the calves; however, there was about 0.5 in. of atrophy of the right thigh. Results of x-ray examinations of the lumbosacral spine were negative, with the exception of the surgical defect and the fusion in the lumbosacral area between L-4, L-5, and S-1. Review of all of his roentgenograms revealed that he had not had an x-ray examination of the pelvis which included both hips. This was taken to complete the series. I found a lesion on the neck and posterior aspect of the femur which was found to be a chondrosarcoma, grade 2, and which was removed.

Case 3.—A man was first seen in 1952, complaining of pain in his back which radiated into his right leg for about four years. There was no history of trauma. He was found to have limitation of motion in the lumbosacral area and muscle spasm of a moderate degree. There was tenderness along the course of the sciatic nerve but none over the sacroiliac. He had a positive straight-leg-raising test result on the right and some hypesthesia over the lateral aspect of the thigh and calf on the involved side. There was full range of motion in the hips, knees, and ankles. Myelograms were taken, and it was thought there might possibly be a degenerated disk between L-4 and L-5 on the involved side. When a laminectomy was performed, a large amount of degenerated disk material was excised and removed at the L-4, L-5 level on the right. The pain subsided in his back and leg, but his gait failed to improve. Three months later it became increasingly difficult for him to flex his thigh, and his straight-leg test result became more positive; however, he still had a full range of motion in the hips, knees, and ankles. Since he had not had a roentgenogram of the pelvis which included the hips, such a film was taken; it showed some cloudiness, which we thought was a lesion in the ilium, superior and posterior to the acetabulum. A biopsy was taken and it was first diagnosed as an osteoid-osteoma but later was shown to be a chondrosarcoma.

Case 4.—The next patient, who was referred to me by another doctor, had an acute onset of pain in his back and gave a history of having had similar attacks previously. He was admitted to the hospital and placed in traction. The laboratory report showed a slight increase in the sedimentation rate but nothing abnormal in the complete blood count or urinalysis. He had marked muscle spasm and limitation of motion of the entire dorsal and lumbosacral spine. The pain radiated into both legs, more marked on the right than the left. He had a strongly positive straight-leg-raising test result, hypesthesia, with occasional numbness, in the right leg, and a diminished knee jerk on the right side. An incidental finding in the x-rays was what seemed to be some punched-out lesions in the scapula. Additional x-rays were taken, and a biopsy was performed on the bone. The patient was found to have multiple myelomas.

Case 5.—A 32-year-old woman developed pain in her back during a pregnancy in the early part of 1958. After delivery of a normal child in the fall she still had pain, which extended down her right leg. When the patient was examined in the hospital in November, 1958, a diagnosis of low back pain with sciatica, probably due to a herniated disk, was made, x-rays were taken, and conservative treatment was instituted. In December her condition had not improved, and a myelogram showed a large defect between L-4 and L-5. A laminectomy was performed in February, 1959, and a large disk. which protruded posteriorly, was removed. She continued to have pain in the back, although the sciatica was much relieved. The pain became more severe, and later she developed sciatica. X-rays taken at this time showed an osteolytic lesion involving the fifth lumbar vertebra. A biopsy specimen taken of the fifth lumbar vertebra proved to be a giant-cell tumor.

Case 6.—A 20-year-old woman had a history of onset of pain in the lower part of her back three days before she was first examined in a clinic in Japan. She was in the fourth month of her first pregnancy. The severe pain was in her back, over the right buttock and radiating down into the right leg, thigh, and knee. She had a positive straight-leg-raising test result on the right, with limitation of motion and muscle spasm in her back and tenderness over the course of the right sacroiliac and right sciatic nerve. She had full range of motion in the hips, knees, and ankles with no atrophy or deformity of the thighs or calves. Results of neurological examinations were negative at that time, with the exception of some hypesthesia over the lateral aspect of the right calf. When the patient returned to the United States the pain in her hip and back had become more severe. On arrival she was walking with a limp and had limitation of motion in all planes of the right hip. X-rays revealed some thinning out and some osteoporosis and decalcification in the region of the right ilium. Biopsy specimens were taken and the diagnosis was reticulum-cell sarcoma.

Case 7.—A 40-year-old woman was first seen in the office in 1955, with a history of several psychiatric episodes over the past few years. She complained of pain in her back, with constant radiation of pain down her left leg, and she was seen by several doctors. Results of examination were essentially negative, with the exception of a diminished ankle jerk on the involved side. Myelograms showed a possible herniated disk between L-5 and S-1 on the left side; however, after several months, she developed weakness in the lower part of the leg and the ankle jerk became completely obliterated. During performance of a laminectomy, I failed to find a herniated disk but I did find some degenerated disk material. The nerve roots in this area had a peculiar appearance. The areas above and below were explored for any possible involvement of the nerve roots but none was found, other than an enlarged ganglion at the lower portion of the fifth lumbar nerve.

After operation, the weakness continued in the lower part of her leg, and she subsequently developed drop foot. A few months later, on reexploration, a large, gelatinous, gray-red tumor was found in the top of the sacrum, about 0.5 in. below the fifth interspace. When this was removed, a medicine glass full of tumor material was obtained. Frozen sections at the time of surgery were reported as nonmalignant; however, on permanent section, it was diagnosed as a neurofibroma. This patient is still alive but is now paralyzed from the fifth lumbar vertebra down. The mass has spread into her pelvis and over areas of her buttocks.

Comment

These patients with extradural osseous lesions simulating the disk syndrome had (case 1) Ewing's tumor of the pelvis; (case 2) multiple myelomas of the lumbosacral spine; (case 3) reticulum cell sarcoma of the right ilium; (case 4) chondrosarcoma of the pelvis; (case 5) chondrosarcoma of the femur; (case 6) neurofibroma of the sacrum; and (case 7) giant-cell tumor of the fifth lumbar vertebra. The patients with Ewing's sarcoma, multiple myelomas, and reticulum cell sarcoma all died within one year of the onset of the symptoms and within one year of the time the diagnosis was made. The patients with chondrosarcoma both died within two years of operation and establishment of correct diagnoses. However, it was obvious that both had had symptoms for as long as five years previously. The patient with neurofibroma is alive but *in extremis*. At present the patient with the giant-cell tumor of the fifth lumbar vertebra is not ambulant and is having neurological difficulties with the lower parts of the legs and difficulty with elimination.

Summary

Seven patients had extradural osseous lesions simulating the disk syndrome. All had symptoms and findings similar to those of an intervertebral disk lesion, with nerve-root irritation, and all at one time or another, had been diagnosed as having such. No surgery was performed on the patients with Ewing's sarcoma, multiple myelomas, or reticulum cell sarcoma, other than for diagnostic procedures. The remaining patients had multiple operations, and it was only after attempts to find an intervertebral disk lesion had been unsuccessful that the correct diagnosis was established. One must conclude that a thorough study of the osseous skeleton should precede any elective surgery of the spine and pelvis.

485 34th St.

CLINICAL NOTES

CRUTCH WITH SLOPING HANDGRIP

Bert C. Wiley, M.D., Johnstown, Pa.

The physical medicine department of Conemaugh Valley Memorial Hospital, Johnstown, Pa., in cooperation with a crutch manufacturer, has made the first major improvement in axillary crutches since the current adjustable crutch was designed about 15 years ago.

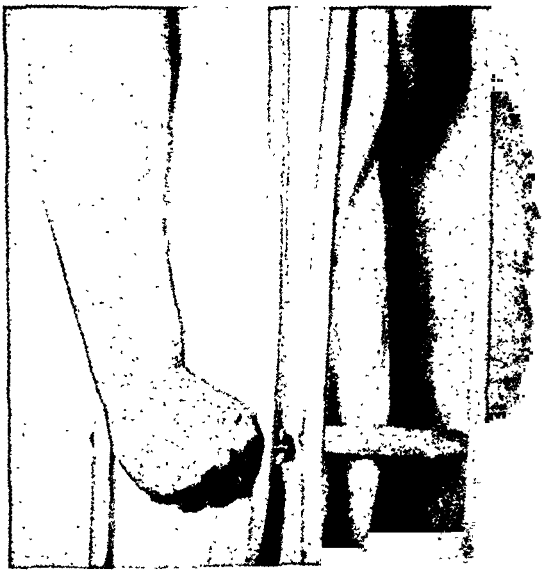

Fig. 1.—Conventional crutch with horizontal handgrip, showing excessive radial deviation of wrist.

Most persons who use axillary crutches quickly develop considerable soreness of the thenar eminence. Some patients have had to return to nonambulatory status because of thumb soreness, when an attempt was made to use crutches too soon. Many persons who routinely use axillary crutches develop painful calluses over the thenar eminence and numbness of the entire thumb. This additional disability is caused by the nonanatomic angle of the crutch handgrip (fig. 1).

When the normal wrist dorsiflexes in order to push against a handgrip, a line across the "heel" of the palm forms an angle of about 60 degrees with the length of the radius. This is at an angle of 30 degrees with the usual horizontal crutch handgrip.

The handgrip of the newly developed crutch (fig. 2) is set at an angle of 15 degrees with the horizontal. This, together with the normal 15 degree flexion of the elbow during crutch weight-bearing, permits the weight-bearing "heel" of the palm to rest evenly on the new handgrip. Even patients with marked deformity of the hand due to rheumatoid arthritis report a very significant increase in hand comfort when using the new crutch. An additional advantage is that it cannot be used "backward" because of the slope of the handle.

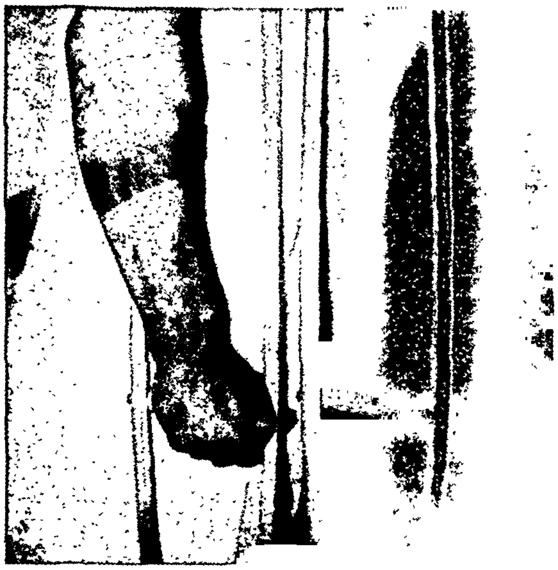

Fig. 2.—New crutch with sloping handgrip, showing normal wrist alignment.

Director of Physical Medicine, Conemaugh Valley Memorial Hospital.

Therefore, the crutch-walker always keeps the wing-nuts forward, where they are less likely to cause injury during a fall. The standard range of adjustment for both crutch length and handgrip distance from the axillary crosspiece has been retained. The new crutches cost only about 25 cents per pair more than the previous conventional adjustable crutches.

A sloping handgrip crutch is not a new idea, since it is an alteration that many hospital shops have been making for two decades.[1]

1086 Franklin St.

Reference

1. Park, H. W.; Malone, E. W.; and Steglich, R.: Tilted Crutch Handpiece, Arch. Phys. Med. **33**:731-733 (Dec.) 1952.

ACUTE POSTOPERATIVE CARDIORESPIRATORY INSUFFICIENCY

TREATMENT BY CURARIZATION AND ARTIFICIAL BREATHING

Paul W. Sanger, M.D., Francis Robicsek, M.D., Frederick H. Taylor, M.D., Robert E. Stam, M.D.,
and
Terry T. Rees, M.D., Charlotte, N. C.

Cardiac insufficiency produces dyspnea. At the same time labored breathing per se compounds the work of the failing heart. This problem challenges the physician every day. The therapeutic approach commonly used to break this vicious cycle is that of decreasing the dyspnea by depressing the respiration. Granted this has advantages, such an approach must be applied cautiously, as excessive depression of respiration may increase the already existing anoxemia.

The introduction, by Björck,[1] of mechanically assisted respiration for acute cardiorespiratory insufficiency was an important therapeutic achievement. Assisted respiration does not, however, completely relieve excessive work of the heart when it is associated with labored breathing. Patients who are uncooperative and those who breathe against the machine may develop fatal exhaustion.

We faced such a problem in one of our patients who underwent direct-vision repair of a large interatrial septal defect complicated by severe pulmonary hypertension. On the third postoperative day he developed acute cardiorespiratory failure which did not respond to the usual therapeutic measures. We attempted to relieve this patient of his severe dyspnea by prolonged curarization and artificial breathing.

Report of a Case

On Feb. 23, 1959, a 10-year-old boy was admitted to the department of thoracic surgery at Charlotte Memorial Hospital. He was known to have had heart disease since birth. At the time of admission the boy was in heart failure and in poor general condition. The clinical examination suggested an interatrial septal defect with pulmonary hypertension and bidirectional shunt. This diagnosis was confirmed by heart catheterization. Right ventricular pressure was 110/6 mm. Hg, and the pressure in the pulmonary artery was 90/38 mm. Hg. His systemic arterial oxygen saturation was 90%. The systemic blood flow was calculated as 2.32 liters per minute, with the pulmonary flow 4.00 liters per minute. The left-to-right shunt at the atrial level was 2.26 liters per minute and the right-to-left shunt 0.58 liters per minute. The pulmonary arteriolar resistance was found to be increased to 810 dyne-cm.$^{-5}$ per second.

After three weeks of intensive medical treatment which included bed rest, administration of digitalis and diuretics, and a low-sodium diet, the patient's condition showed moderate improvement. His peripheral edema disappeared; his liver became smaller, and his dyspnea at rest ceased. It was decided to repair the interatrial communication.

At operation the heart was found to be enormously enlarged and the pulmonary artery was about three times larger than the aorta. Cardiopulmonary bypass was begun[2] and the right atrium was entered. We found a secundum type of septal defect, about 3 cm. in diameter. Two-thirds of this defect was closed, but one-third was left open as an emergency vent for the overloaded right ventricle. The patient tolerated the 15 minutes of total body perfusion. His first postoperative day was uneventful.

On the night of the second day after the operation the patient developed excessive bronchial secretions. Intratracheal suction was performed repeatedly. Blood pressure and pulse rate remained relatively stable, and his color was good.

From the Department of Thoracic Surgery and the Heineman Cardiopulmonary Research Laboratory, Charlotte Memorial Hospital.

On the third postoperative day the patient's general condition showed progressive deterioration. *Portable chest x-ray film revealed partial atelectasis* of both lungs. A tracheostomy was performed. Late in the morning he had two attacks of pulmonary edema and his dyspnea became extremely severe. The blood pressure fell to 65 mm. Hg systolic, and the pulse rate was 160 per minute. Bronchoscopic aspiration was performed through the tracheostomy, the dosage of digitalis was increased, and infusion of phenylephrine (Neo-synephrine) hydrochloride was started. The tracheostomy cannula was attached to a Bennett respirator, but failure of the patient to cooperate forced us to discontinue this assisted breathing. During the afternoon the patient developed mediastinal emphysema and tension pneumothorax, both of which were decompressed immediately by performance of water-sealed intercostal catheter drainage.

During the evening of the third postoperative day the patient's condition became critical. Peripheral pulses could not be felt; the heart rate was 200 per minute. He was extremely cyanotic and was struggling desperately for air with his remaining physical power. The patient was placed in a Drinker respirator and 15 mg. of tubocurarine chloride was administered intravenously. All voluntary muscular activity ceased immediately, and the patient was given artificial respiration. Within an hour the cyanosis completely disappeared, the pulse rate slowed to 120 per minute, and the blood pressure rose to 90/60 mm. Hg. Small doses of curare were administered intravenously whenever the patient showed voluntary muscular activity. The next morning his blood pressure was 110/80 mm. Hg, with the pulse rate 105 per minute. He had no further attacks of pulmonary edema and his color remained good.

The patient was kept completely paralyzed by administration of curare, and artificial respiration was given for 48 hours. Thereafter the dosage of curare was gradually decreased. The patient remained well accommodated to the breathing rhythm *of the machine.* The next day he was removed from the respirator. His breathing was then assisted by a Bennett machine for an additional four days. His condition remained satisfactory; he had no dyspnea or cyanosis at rest and left the hospital on the 30th postoperative day in good condition. The patient has been closely observed since discharge. He has remained well compensated.

Summary

A 10-year-old boy underwent open cardiotomy because of a large interatrial septal defect, with pulmonary hypertension and bidirectional shunt. The patient developed acute cardiorespiratory insufficiency on the third postoperative day.

Despite active therapeutic management his condition became critical. To relieve the patient of his extremely severe dyspnea and provide adequate gas exchange, he was placed in a respirator and complete musculoplegia was induced by prolonged administration of curare. The patient improved rapidly. He was kept in a respirator while curare was administered for a period of 48 hours, after which he showed satisfactory recovery.

Doctors Building, Kings Drive (7) (Dr. Sanger).

This study was supported in part by the John A. Hartford Foundation and the United Medical Research Foundation of North Carolina.

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1. Björck, V. O., and Engström, C. G.: Treatment of Ventilatory Insufficiency After Pulmonary Resection with Tracheostomy and Prolonged Artificial Ventilation, J. Thoracic Surg. **30:**356-367 (Sept.) 1955.

2. (*a*) Sanger, P. W., and others: Experiences with Direct-Vision Repair of Congenital Cardiovascular Disorders Using Rotating Disc Oxygenator, North Carolina M. J. **20:** 89-95 (March) 1959. (*b*) Björk and Engstrom.[1]

3. Sanger, P. W., and others: Some Problems in Open Heart Surgery, to be published.

TONS OF PESTICIDES.—The use of parathion as an insecticide started during the second world war. It was first sold in Finland in 1950 and by 1957 the total of parathion preparations sold had risen to 160 tons. Nearly two-thirds of all pest extermination on farm and garden now employs pesticides containing parathion. . . .

To obtain an idea of the significance of the number of fatal cases due to parathion pesticides, we can mention by way of example that in Finland pregnancy, parturition, and puerperal complications were the cause of death of 94 persons in 1955, 99 in 1956, and 77 in 1957. Again, deaths from poliomyelitis in 1956, when mortality from this disease was at its highest, were 37. . . . In Finland between 1952 and 1957 there were 286 deaths from parathion pesticides used in agriculture and horticulture. In 1957 the number had risen to 105; 237 of the total deaths were by suicide. Only 20% of these cases had an opportunity of procuring the poison for their work. The sale of parathion preparations should be more strictly controlled.—T. Toivonen, M.D., K. Ohela, M.D., W. J. Kaipainen, M.D., Parathion Poisoning Increasing Frequency in Finland, *The Lancet,* Aug. 22, 1959.

COUNCIL ON DRUGS

Report to the Council

The Council has authorized publication of the following report.

H. D. Kautz, M.D., *Secretary.*

CURRENT STATUS OF THERAPY OF BRUCELLOSIS IN HUMAN BEINGS

Wesley W. Spink, M.D., Minneapolis

The successful management of brucellosis in human beings depends on a recognition of certain basic features of the disease. Brucellosis is caused by one of three species of brucellae, namely, Brucella abortus, Brucella melitensis, and Brucella suis. This distinction is important because the natural course of the disease differs in severity according to the species of brucellae that has invaded the tissues. Illness caused by Br. abortus is less severe than that caused by the other two species. This form of brucellosis is most prevalent in the United States. Disease resulting from Br. melitensis is more serious and is characterized by prostration, complications, and chronicity. Br. melitensis is the cause of most brucellosis in human beings, worldwide. The outstanding feature of brucellosis due to Br. suis is a debilitating and prolonged febrile illness, with complicating suppurating lesions of the bone and viscera. Brucellosis caused by Br. suis is prevalent in certain areas in the United States where large numbers of swine are raised.

Another basic factor in the management of brucellosis is the necessity for establishing a precise diagnosis of active disease before starting therapy. This requires careful bacteriological and serologic studies. When infection cannot be established bacteriologically by culture, the results of brucella sero-agglutination tests must be cautiously interpreted. In general, agglutination titers of 1:100 or over are consistent with active disease. Lower titers are often of doubtful significance, especially when these low titers are found with repeated tests. When bacteriological cultures remain sterile and brucella agglutinins are absent or present only in a low titer, a positive intradermal brucella test is of doubtful diagnostic value. The brucella skin test is specific and indicates past exposure to the disease, but a positive test does not connote active brucellosis.

One added feature of brucellosis requires elucidation. Brucellosis may have a severe impact on the nervous system. Weakness and mental depression are common manifestations. An emotionally unstable person may be plunged into a severe depression after an acute brucella infection. He may be mistakenly subjected to "antibrucella therapy" for several years instead of having efforts directed toward correcting the underlying psychosomatic disturbance. On the other hand, it is also a grave error to subject a patient with undetected active brucellosis to psychotherapy. The correlation of neurological and psychic disturbances with brucellosis should be kept in mind.

After the diagnosis of active brucellosis has been established, the patient should be informed that brucellosis is a self-limited disease. The patient is not encouraged when he is told that brucellosis can result in a chronic debilitating illness; however, brucellosis causes disabling chronic illness in relatively few patients. The emotional pattern of the patient must be carefully surveyed, since his ultimate restoration to good health will often depend on this factor. For the most part, brucellosis is an occupational disease, and the interpretation of chronic illness can be the result of disability insurance.

Specific Measures

The patient with active brucellosis should engage in a minimum of physical activity. The toxic and febrile patient should be kept in bed. Somatic pains and headaches can be alleviated with salicylates, although the nocturnal sweats associated with brucellosis can be accentuated by therapy with salicylates. Insomnia and nervousness during the acute illness can be relieved with sedatives.

It has been established in experimental brucellosis and in man that antibiotics will suppress the infection, reduce complications, and shorten the course of the disease. The tetracycline drugs, chlortetracycline (Aureomycin) hydrochloride, oxytetracycline (Terramycin) hydrochloride, or tetracycline (Achromycin, Panmycin, Polycycline, Steclin, Tetracyn) hydrochloride, constitute the treatment of choice and are recommended in an oral dose of 500 mg. every six hours for a minimum of 21 days. If the patients tolerate the drug well, this same

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From the Department of Medicine, University of Minnesota Medical School.

therapeutic regimen can be repeated within six to eight weeks, if a relapse should occur. It is not unusual for patients to have a relapse of their illness two to three weeks after the completion of an initial course of tetracycline therapy, especially with disease caused by Br. melitensis. In the more severe cases, 1 to 2 Gm. of streptomycin daily for 14 days should be simultaneously administered intramuscularly. In some instances, the disease may relapse two and three times before recovery takes place. One of the tetracyclines should be used for 21 days for each relapse. It is very doubtful if more than three courses of antibiotic therapy are beneficial, except in the rare patient in whom demonstrable suppuration is present.

Patients exhibiting a severe toxic state may have an accentuation of their illness shortly after an initial dose of antibiotic. This systemic reaction can be so severe that peripheral vascular collapse occurs. This unfavorable reaction is presumed to be due to the antibrucella action of the drug liberating brucella antigen (endotoxin) in a patient with acquired brucella hypersensitivity. This reaction can be prevented by administering corticotropin (Acth, Acthar, Corticotropin) or one of the glucocorticoids with the antibiotic. A suspension of corticotropin can be given intramuscularly in a dose of 40 mg. every eight hours. Cortisone (Cortisone, Cortogen, Cortone) acetate is given orally in a dose of 100 to 300 mg. three times daily or prednisone (Deltasone, Deltra, Meticorten, Paracort) in an oral dose of 20 mg. three times daily. Steroid therapy also is beneficial in the seriously ill patient. The initial Herxheimer-like reactions can also be avoided by use of small initial doses of antibiotics. The toxemia and febrile state gradually subside over a period of several days when antibiotics alone are used, but, when steroid drugs are also employed, the patient improves within 24 hours. Treatment with steroids should not be continued for more than 72 hours and should be restricted to the more seriously ill patients.

Although brucella vaccines are used for brucellosis in human beings, there is no general agreement concerning their value. Vaccine has usually been employed in the treatment of chronic brucellosis. The attempt is made to desensitize patients to brucella antigen by intermittent parenteral injections of the material over a long period of time. Unfortunately, the results are difficult to evaluate, and the vaccines cause considerable discomfort and expense to the patient. Vaccine has also been recommended for the more acutely ill patients, along with antibiotics. The vaccine is given intravenously in a dose that will provoke a systemic febrile reaction. This procedure is dangerous since peripheral vascular failure can occur. Until more definitive evidence is at hand, vaccine therapy cannot be recommended for either "desensitizing" purposes or for the purposes of inducing a pyrogenic response.

Chronic Brucellosis

One of the problems that perplexes clinicians is the management of patients with so-called chronic brucellosis. These persons express subjective complaints consistent with chronic illness, but objective evidence of disease is often not apparent. Lacking either bacteriological or significant serologic proof of activity, these patients are not infrequently subjected to long courses of vaccine therapy. They usually have a positive dermal reaction for brucella antigen. In addition to vaccine, they may also receive one or more courses of antibiotic therapy. The precise diagnosis is usually in doubt, and the results of therapy may be dubious.

Comment

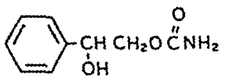
At present, neither vaccine nor antibiotic therapy can be recommended for acute or chronic illness unless the diagnosis of brucellosis can be supported by dependable bacteriological or serologic data. Subjective complaints, with or without a positive brucella skin test, do not constitute sufficient evidence for a diagnosis of active brucellosis.

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. Kautz, M.D., *Secretary*.

Styramate (Sinaxar).—2-Hydroxy-2-phenylethyl carbamate.—The structural formula of styramate may be represented as follows:



Actions and Uses.—Styramate displays a pattern of pharmacological activity in animals similar to that of mephenesin and other centrally acting skeletal muscle relaxants. Thus, experimental observations indicate that it is a central nervous system depressant with relative specificity in depressing polysynaptic spinal reflexes; it antagonizes convulsions induced either by drugs or by electroshock. After oral administration, the duration of action of styramate seems to be two or three times that of mephenesin. In animals, toxic doses produce decreased motor activity, ataxia, loss of the righting reflex, and paralysis. Chronic toxicity studies have revealed no adverse effects on the liver, kidney, or blood-forming tissues.

Of the reported clinical trials of styramate, few have incorporated comparisons with other muscle relaxants or with placebos. The present assessment of the efficacy of the drug must, therefore, be regarded as tentative. However, although much more experience or more carefully designed clinical investigation will be required to establish the value of styramate, the limited available evidence indicates that it may be helpful in relieving muscle spasm associated with a variety of clinical conditions, including myositis, fibrositis, arthritis, spondylitis, acute lumbosacral strain, and torticollis. It should be considered an adjunct to physiotherapy and other appropriate measures. The drug is not claimed to be effective in paralysis agitans.

Although drowsiness, vertigo, headache, and urticarial eruption have been reported after administration of styramate, the incidence of these side-effects was low, and their occurrence cannot be definitely ascribed to the use of the drug. Patients should be cautioned concerning a possible sedative effect, however.

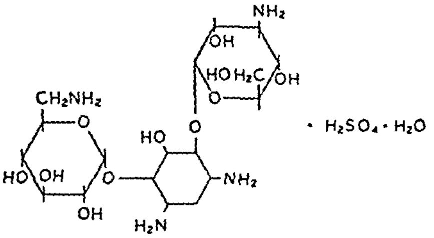
Dosage.—Styramate is administered orally. The dose is adjusted in accordance with the needs and tolerance of the individual patient. Although larger doses have been used, 200 mg. four times daily should be tried initially. If the response is unsatisfactory, the dose may be gradually increased, as required, until a total daily dosage of 1.6 Gm. is reached, unless untoward effects supervene.

Preparations.—tablets 200 mg.

Year of introduction: 1958.

Armour Pharmaceutical Company, Division of Armour and Company, cooperated by furnishing scientific data to aid in the evaluation of styramate.

Kanamycin Sulfate (Kantrex).—The sulfate salt of an antibiotic substance derived from strains of Streptomyces kanamyceticus.—Kanamycin is a thermostable, water-soluble, polybasic substance. Its chemical structure consists of two amino sugars glycosidically linked to deoxystreptamine. The chemical structure of kanamycin sulfate may be represented as follows:



Actions and Uses.—The in vitro antibacterial activity of kanamycin is almost identical with that of neomycin. Kanamycin is active against many aerobic gram-positive and gram-negative bacteria, including most of the strains of staphylococci so far isolated from clinical sources. Gram-negative organisms sensitive to kanamycin include species of Klebsiella, Aerobacter, Shigella, Salmonella, Neisseria, Escherichia coli, and the majority of strains of Proteus. It is active against mycobacteria. Common gram-positive pathogens such as streptococci and pneumococci are usually resistant to kanamycin at concentrations attainable in body fluids. Enterococci, Brucella, and Pseudomonas organisms are generally resistant as are clostridia, bacteroides, yeasts, and fungi. It is recommended that clinical therapy with kanamycin be guided by in vitro antibiotic sensitivity tests whenever possible.

The development of bacterial resistance to kanamycin can be demonstrated in vitro and in vivo against most sensitive organisms so far tested. There is almost complete cross resistance of organisms to neomycin and kanamycin and one-way cross resistance between streptomycin and kanamycin; i. e., organisms made resistant to kanamycin are resistant to streptomycin, but organisms made resistant to streptomycin are sensitive to kanamycin. In the case of the mycobacteria, cross resistance does not exist between kanamycin and streptomycin. Mycobacteria exhibit similar one-way cross resistance between viomycin and kanamycin. Kanamycin probably is bactericidal against most of the sensitive organisms; it is more active under aerobic than anaerobic conditions. The mechanism of action has not been fully elucidated. Against mycobacteria, kanamycin is bacteriostatic rather than bactericidal; mycobacteria develop resistance as rapidly as with streptomycin. Bacterial resistance can be induced among sensitive staphylococci, but it occurs in a slow, step-wise fashion as is the case with penicillin.

Kanamycin is absorbed rapidly from intramuscular sites but only slightly absorbed from the gastrointestinal tract. Hence, kanamycin must be used parenterally for systemic infections. After intramuscular injection, the drug is absorbed rapidly, inducing peak serum concentrations within one hour after injection. Blood levels from recommended doses are maintained for 8 to 12 hours. Kanamycin does not cross the blood-brain barrier in persons without meningeal infection at doses so far used, but it may reach significant concentration if the meninges are inflamed. Kanamycin appears in pleural, peritoneal, and synovial fluids after intramuscular injection.

Kanamycin is not recommended in minor or self-limited infections and should be used cautiously in the presence of renal impairment because of the increased risk of ototoxicity in such patients; in moderately severe or severe infections which are about equally susceptible to more than one antimicrobial agent, including kanamycin, the choice of therapy should be determined on the basis of relative potentiality for inducing serious toxic effects. Because of the lack of cross resistance between kanamycin, penicillin, streptomycin, chloramphenicol, novobiocin, oleandomycin, and the tetracyclines, kanamycin may be useful in infections which have failed to respond to those antibiotics. There appears to be no doubt that kanamycin has been lifesaving in those instances in which organismal resistance precludes the use of other antimicrobials.

Parenteral therapy with kanamycin has been successfully used in patients with staphylococcic and gram-negative infections of the respiratory tract, soft tissues, and the urinary tract as well as in osteomyelitis, septicemia, and bacteremia. Kanamycin may be given orally for infections of the gastrointestinal tract due to sensitive organisms, particularly Salmonella and Shigella; severe infections may require supplemental parenteral therapy. Kanamycin may be used for preoperative preparation of the large intestine in the same manner as neomycin. It has also been used orally to destroy nitrogen-producing bacteria as a means of reducing blood ammonia levels in cirrhotic patients suffering from hepatic coma. Limited clinical experience indicates that kanamycin given orally may be effective in eliminating cysts of Entamoeba histolytica from the stools of asymptomatic carriers.

Kanamycin has been given in a 2.5% concentration by intraperitoneal instillation after exploration for established peritonitis or after contamination due to fecal spill during surgery. The usefulness of this procedure is not established because of the danger of respiratory paralysis when the patient is still under the effects of anesthetics or muscle relaxants and because of the possibility of renal damage if the patient goes into shock. The drug has also been used as an irrigating solution (0.25%) in abscess cavities, in the pleural space, and in the peritoneal and ventricular cavities.

Kanamycin is not now recommended for the treatment of tuberculosis. However, clinical investigation programs are in progress, which should point out the proper place of kanamycin in therapy of tuberculosis.

Limited clinical studies indicate that kanamycin is effective in cutaneous anthrax and in acute gonorrhea in the male, but it is not recommended for these infections because less toxic antimicrobials are equally effective.

Toxicity and Side-Effects.—The major toxic effect of parenterally administered kanamycin is its action on the auditory portion of the eighth nerve. This effect seems to be related to the height and duration of serum concentrations of kanamycin. For this reason, the recommended daily dose of 15 mg. per kilogram of body weight should not be exceeded except in rare instances, nor should the duration of therapy be prolonged unnecessarily. Ototoxic reactions are much less frequent in well-hydrated patients under 45 years of age with normal kidney function who receive less than 20 Gm. of kanamycin in 10 to 14 days and who have not previously received streptomycin, dihydrostreptomycin, or neomycin. The drug should be used with extreme caution and in considerably reduced dosage in patients with impaired renal function, since delayed excretion of the drug induces unnecessarily high serum levels and sharply increases the risk of ototoxicity. The risk of ototoxicity is also greater in patients beyond middle age. Deafness can be either partial or complete and, in most cases, has been irreversible.

Hearing loss is sometimes preceded by tinnitus or dizziness. If these symptoms occur, the drug should be withdrawn immediately. In patients with impaired renal function, hearing loss and even total deafness has occurred two to seven days after the drug has been withdrawn. This appears to be due to the maintenance of high serum levels because of failure of excretory mechanisms. If kanamycin is to be used in the treatment of infections in patients who have renal impairment, the daily dosage should be reduced by as much as one-quarter or one-half the total daily dosage. If possible, the patient's hearing should be checked with the audiometer before and during treatment, and kanamycin therapy should be stopped if there is loss of high frequency response.

Evidence of renal irritation (casts, albumin, and microscopic hematuria) frequently occurs during parenteral therapy with kanamycin. This seems to be associated with the rapid excretion of the drug by glomerular filtration and selective reabsorption of water (but not of kanamycin) in the tubules. These effects appear to be reversible on cessation of therapy and are not indications for withdrawing kanamycin if the patient's infection is responding. In some patients with concurrent renal failure, particularly those suffering from intercapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome), kanamycin may be nephrotoxic. Increasing elevation of the blood urea nitrogen level or the appearance of oliguria are indications for stopping kanamycin therapy.

Some local irritation or pain may follow intramuscular injection, but this has rarely interfered with continued therapy. Eosinophilia has been noted. Among the minor side-effects to the drug are rare instances of sensitization, skin rash, drug fever, headache, and paresthesia. Neither hematopoietic nor hepatic toxicity has been noted, either in animal studies or during clinical use.

Because of its slight absorption from the gastrointestinal tract, oral administration is generally well tolerated and without significant side-effects. The possibility of absorption of kanamycin from ulcerated intestinal lesions or retention due to shock or renal damage should be borne in mind, but ototoxicity after oral administration is unlikely and has not been reported.

Dosage.—Kanamycin sulfate is given by intramuscular injection, but it also may be administered intravenously for systemic effect. For local or topical effect, kanamycin may be administered orally, intraperitoneally, by inhalation as an aerosol, and by intracavitary instillation. Dosage is expressed in terms of the free base. Patients receiving systemic kanamycin therapy should be well hydrated.

For intramuscular administration in adults and children, the daily dosage should not exceed 15 mg. per kilogram of body weight given in two or three divided doses. If infection is not controlled within five days, the clinical picture should be reevaluated.

The intravenous injection of kanamycin sulfate is recommended only for gravely ill patients with overwhelming infections or with impending vascular collapse. When indicated, a 0.25% solution (2.5 mg. per cubic centimeter) is prepared and administered by slow intravenous infusion at a rate of 3 to 4 cc. per minute. The dosage for adults and children is 15 to 30 mg. per kilogram of body weight per day given in two or three divided doses.

For intraperitoneal use after surgery in patients with peritonitis or fecal contamination of the peritoneum, 2.5% solutions (500 mg. of kanamycin in 20 cc. of water for injection) have been instilled through a polyethylene catheter sutured into the wound at closure.

For inhalation (aerosol) therapy in patients with respiratory tract infections, a solution containing 250 mg. in 1 cc. is diluted with 3 cc. of sodium chloride injection and nebulized.

For intracavitary use, a 0.25% irrigating solution (2.5 mg. per cubic centimeter) has been instilled in abscess cavities, pleural space, and peritoneal and ventricular cavities. Small amounts should be used: the volume given intrathecally or into the ventricles should probably not exceed 5 cc.

For preoperative preparation of the large intestine, kanamycin is given orally in doses of 1 Gm. every hour for four hours, then 1 Gm. every six hours for 36 to 72 hours before surgery. For oral use in the treatment of Shigella and Salmonella infections, total daily dosage has ranged from 15 to 30 mg. per kilogram of body weight. In amebiasis, oral dosage has ranged from 30 to 150 mg. per kilogram of body weight per day given in divided doses for 10 days.

It must be emphasized that kanamycin should be given orally only for the purpose of obtaining antibacterial effects within the intestine; it should not be given orally for systemic infections.

Preparations.—capsules 500 mg.; solution (injection) 500 mg. in 2 cc., 1 Gm. in 3 cc.

Year of *introduction:* 1958.

Bristol Laboratories Inc. cooperated by furnishing scientific data to aid in the evaluation of kanamycin sulfate.

Buccal and Intramuscular Use of Streptokinase-Streptodornase (Varidase)

The Council has reviewed the available evidence pertaining to the usefulness of buccally or intramuscularly administered streptokinase-streptodornase for the treatment of edema associated with inflammation or infection. (For a description of topical or intracavitary therapy with this enzyme preparation in the management of suppurative conditions in which infection or purulent exudation is present, see the monograph on streptokinase-streptodornase in New and Nonofficial Drugs.) It is postulated that the beneficial effects of buccally and intramuscularly administered streptokinase-streptodornase are due to the streptokinase component of the mixture and are explained by the ability of this enzyme to liquefy fibrin thrombi through activation of plasmin in blood and lymphatic channels and by lessening the viscosity of edema fluid. It is claimed that streptokinase permits easier access of the humoral forces of the host and concomitantly administered antibiotics to the area of infection. Although this may be theoretically plausible, the experimental observations in animals are incapable of establishing such a mode of action.

Among the conditions for which streptokinase-streptodornase may prove useful are those that may be associated with acute inflammatory processes, such as thrombophlebitis; cellulitis; abscess; sinusitis; arteriosclerotic, varicose, and stasis ulcers; hematoma; contusions; the congestion associated with bronchitis and bronchiectasis; sprains; fractures; dental surgical procedures, and any form of trauma. Clinical experience with buccally or intramuscularly administered streptokinase-streptodornase has been extensive, and many favorable results have been reported. Relief of pain, quicker resolution of edema, and more rapid subsidence of infection are said to follow its use. However, few of the studies have been well controlled. This seriously hampers a precise evaluation of the drug. Due to the variable course (with or without treatment) of the conditions for which streptokinase is proposed, it is difficult to assess, in the absence of carefully controlled studies, what part in the over-all improvement of the patient may be ascribed to the drug. In patients with edema associated with infection, streptokinase-streptodornase should be administered concomitantly with antibiotics. Comparative observations, with placebo medication substituted for the enzymes, would be difficult to carry out. However, in the absence of such studies, it is not possible to determine whether enzyme therapy was a contributing factor in the accelerated improvement of the patients. Clinical observations would tend to support the conclusion that the adjunctive use of streptokinase-streptodornase by either the buccal or intramuscular routes has a useful place in the management of inflammatory edema, with or without infection. The evidence presented to support this conclusion does not, however, withstand critical scrutiny. Accordingly, in the judgment of the Council, the usefulness of the drug by these routes of administration is unestablished.

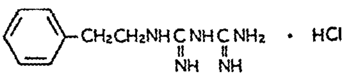
When administered by the buccal route, streptokinase-streptodornase is well tolerated. Side-effects have been limited to urticaria, skin rashes, and rare instances of local irritation and dryness at the site of tablet disintegration. When the drug is given intramuscularly, pain at the site of injection has been observed in many patients. Febrile reactions have also followed its parenteral injection; as with any parenterally administered foreign protein, there is a theoretical risk of serious allergic reactions. By either route, caution is advised when there is evidence of a defect in blood coagulation or impairment of liver function.

For buccal use, a tablet containing 10,000 units of streptokinase is placed in the buccal pouch or under the tongue and allowed to dissolve slowly. The usual dose is one tablet four times daily. The tablets should not be chewed or swallowed whole. For intramuscular use, a solution is prepared from the streptokinase-streptodornase mixture which provides 10,000 units of streptokinase per cubic centimeter. The proposed dose is 0.5 cc. (5,000 units of streptokinase) injected twice daily in the gluteal region. Although the evidence that streptokinase-streptodornase exerts a beneficial effect is inconclusive, the foregoing doses may be regarded as a base line or guide.

The Council voted to expand the monograph in New and Nonofficial Drugs to describe the buccal and intramuscular use of streptokinase-streptodornase, with caution as to the experimental status of these routes of administration.

Lederle Laboratories Division, American Cyanamid Company, cooperated by furnishing scientific data to aid in the evaluation of the buccal and intramuscular use of streptokinase-streptodornase.

Phenformin Hydrochloride (DBI).—N^1-β-Phenethylbiguanide hydrochloride.—The structural formula of phenformin hydrochloride may be represented as follows:


C_6H_5-$CH_2CH_2NH\overset{}{\underset{NH}{C}}NH\underset{NH}{C}NH_2 \cdot HCl$

Actions and Uses.—Phenformin hydrochloride is an orally effective hypoglycemic agent used in the management of diabetes mellitus. A biguanide derivative, it should not be confused with the distinctly different diguanidine compounds, some of which also have hypoglycemic activity but which may produce renal and hepatic damage. Nor is it related chemically to the sulfonylurea compounds, such as tolbutamide, or to insulin.

Phenformin hydrochloride may be used alone, in conjunction with insulin, or with other antidiabetic agents. It has a somewhat wider spectrum of usefulness than the sulfonylurea derivatives, but, like the latter, it is a much less potent hypoglycemic agent than is insulin; when used alone, it effects normoglycemia and eliminates glycosuria in only a portion of the patients in whom it is tried. The patients in whom it is most likely to be effective are those in whom the disease is stable, is of recent onset, began after the onset of maturity, requires only small doses of insulin, and has never been complicated by acidotic ketosis. In an additional group of patients whose symptoms cannot be satisfactorily controlled by administration of sulfonylurea or biguanide derivatives alone, the concomitant use of these two groups of oral agents may render supplemental insulin unnecessary. Finally, unlike the sulfonylurea compounds, it is also effective in a few cases of labile diabetes and of juvenile diabetes, although most patients in these groups will continue to require insulin.

Phenformin hydrochloride alone is only occasionally effective in diabetes requiring more than 40 units of insulin per day. It should not be used in diabetes that is controlled by diet alone, in juvenile diabetes that is well regulated by insulin, in the management of diabetes during the early postoperative period, and in such complications of diabetes as acidosis, coma, and infection. In stable diabetes, phenformin hydrochloride offers an advantage over insulin only when it is effective alone, since little is gained by a mere reduction in the dose of insulin. In unstable diabetes, on the other hand, the conjunctive use of phenformin hydrochloride and insulin may be justified, since the concomitant use of the two drugs sometimes effects smoother regulation than the use of either alone.

That phenformin hydrochloride lowers blood sugar level and eliminates glycosuria in many patients is undeniable; whether it corrects the underlying defects in carbohydrate, fat, and nitrogen metabolism, however, is still unknown. Thus, it is somewhat disturbing that some patients in whom phenformin hydrochloride maintains a normal blood sugar concentration may experience loss of weight, weakness, and lassitude unless small doses of insulin are also administered. Too, the effects of phenformin hydrochloride on the vascular and other long-term sequelae of diabetes can be determined only after years of experience. For these reasons, patients receiving this relatively new drug must be most attentively observed for both acute and long-term complications.

Phenformin hydrochloride, like other oral hypoglycemic agents and like insulin, controls rather than cures diabetes mellitus. It does not obviate the need for complete education of the patient concerning his disease and its treatment. The importance of adherence to a carefully formulated diet and of the prevention and treatment of diabetic complications must still be stressed. All patients must be instructed in the use and injection of insulin, since this drug remains the indispensable agent for the treatment of the acute complications of diabetes mellitus.

Side-Effects.—The usefulness of phenformin hydrochloride is limited by the frequency with which gastrointestinal symptoms such as anorexia, nausea, vomiting, and diarrhea occur. The incidence and severity of these symptoms are proportional to the dose. Although they occur in about 25% of patients receiving 150 mg. or more per day, an occasional patient may tolerate much larger doses. These and other minor side-effects are reversible and ordinarily disappear within 24 hours after the drug is withdrawn. Adverse effects on the liver, kidney, or hematopoietic tissues or other serious toxicity have not been reported.

Pharmacology.—In therapeutic doses, phenformin hydrochloride has few effects other than its hypoglycemic action. Adrenal function, as measured by 17-ketosteroid and 17-hydroxycorticoid urinary excretion, is not altered; response to adrenocorticotropic hormone remains unchanged. Nor does there appear to be any effect on thyroid function; although uptake of iodine by the thyroid may increase slightly in some patients, there is no alteration of serum protein-bound iodine or of cholesterol concentration. The blood concentrations of pyruvic acid and lactic acid may increase slightly in diabetic patients but usually remain unchanged when the drug is given to normal persons.

Phenformin hydrochloride is apparently absorbed satisfactorily from the gastrointestinal tract. Its time-action curve has not been described in detail in human beings, but experiments in animals suggest that it has a relatively brief duration of action, with the peak effect occurring three to five hours after administration of a single dose. The metabolic fate and routes of excretion of the drug are unknown.

Evidence concerning the mechanism of action of phenformin hydrochloride is conflicting. That insulin-secreting tissue is not necessary for its action is clear, since the drug lowers the blood sugar in depancreatized animals, although to a lesser degree than in the intact animal. The effect is also observed in the animal made diabetic by treatment with alloxan and in the hepatectomized animal. Phenformin hydrochloride does not lower the blood sugar level in nondiabetic man. The greater part of the present evidence suggests that its most important action is to increase the rate of anaerobic metabolism of glucose. There is some evidence that a decrease in gluconeogenesis and an increase in the oxidation of glucose via the hexose monophosphate shunt may also occur. Although phenformin hydrochloride, like many other drugs, inhibits the degradation of insulin in vitro, it seems unlikely that this action contributes significantly to its effects in vivo.

Dosage.—Phenformin hydrochloride is administered orally. As with any agent used in the management of diabetes, the dose must be adjusted to meet the needs of the individual patient. The drug may be given with meals in an attempt to minimize gastrointestinal side-effects, although there is no evidence that these effects are due to local irritation. Two or three doses a day will produce satisfactory results in many patients, but four doses a day will often afford smoother regulation of the blood sugar level. The dose should be low initially and increased gradually. Although there is no contraindication to the use of larger doses in patients who require and tolerate them, the incidence of gastrointestinal side-effects is quite high when the total daily dose exceeds 150 mg. It should be remembered that, with a given dosage schedule, significant hypoglycemic response may not be apparent until after a period of three days or more.

Hospitalization facilitates proper dosage adjustment. The effect on blood sugar level, urine sugar level, and ketone bodies must be carefully observed. Should signs of acidotic ketosis, impending coma, or other complications appear, the insulin dosage must be immediately increased and other appropriate therapeutic measures instituted.

In diabetics who have never received insulin, but in whom the disease cannot be satisfactorily controlled by diet alone, phenformin may be started in initial doses of 25 mg. twice daily. If the response is not satisfactory, the daily dose is increased by increments of 25 mg. at intervals of three or four days.

In patients who are receiving insulin, the dose of phenformin hydrochloride is gradually increased as the dose of insulin is reduced. The dose of phenformin hydrochloride that will be needed cannot be predicted from the insulin requirement. In all cases, the initial dose of phenformin hydrochloride is 25 mg. twice a day; again, the total daily dose is increased in increments of 25 mg. at intervals of three or more days, as required. In adults with stable diabetes, who require less than 30 units of insulin per day, the insulin may be withdrawn at once, or, if preferred, the dose may be reduced gradually; if the daily insulin requirement exceeds 30 units per day, however, the insulin dose should not be reduced by more than 25% at one time.

In labile or juvenile diabetes, usual doses of insulin are continued for several days after treatment is begun. The dose of insulin is then reduced very slowly; each reduction should not exceed 10%. In these cases, complete withdrawal of insulin is ordinarily impossible, so that the usual objective is smoother regulation than is possible with the use of insulin alone.

Preparations.—tablets 25 mg.

Year of introduction: 1959.

U. S. Vitamin & Pharmaceutical Corporation, Division of Arlington-Funk Laboratories, cooperated by furnishing scientific data to aid in the evaluation of phenformin hydrochloride.

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THE CHEMISTRY OF ANTIBIOTICS

THE chemotherapeutic properties of penicillin which were revealed by serendipity, followed by the discovery of streptomycin after years of critical investigation, appeared to be remotely related areas in microbiology. During the past decade the tremendous volume of research that has been pursued throughout the world in gathering additional information as well as the identification of new compounds which resulted in the synthesis recently of penicillin has unfolded a fascinating plan of biological action and cellular metabolism. The trail of investigative efforts led not only to the development of antibiotics such as chloramphenicol, the tetracyclines, and erythromycin but also to the revelation of compounds that are effective against infection by selected fungi. There is yet another column in the rapidly changing kaleidoscope that may be equally significant. The selective inhibition of the growth of tumor cells or viruses that contribute to the metaplasia of cells has resulted in no immediate therapeutic possibilities, but the long-term results in this endeavor may be critical for the understanding of the pathogenesis of malignant life.

Investigations into the microbiology of the actinomycetes, a filamentous bacteria isolated from the soil, which may produce actinomycosis, lumpy jaw in man and animals, have been particularly promising. It is a strange phenomenon that some parasites attack other parasites and also that suppression of some types of infection enhances the growth of others and permits the emergence of antibiotic-resistant strains. Were it not for this second action, investigations into the microbiology of antibiotics might well be progressing at a much slower pace. Furthermore, if the discoveries of the first decade of the antibiotic era had produced maximally effective agents without such serious handicaps, specific studies that concern cellular metabolism as noted below might not have been pursued.

Although the antibiotics embrace a wide variety of compounds, there is selective relationship structurally among the several groups. Penicillium chrysogenum is capable of synthesizing a number of penicillins which differ in the side chain only, depending on the precursor of the side chain that was added to the culture medium. Streptomyces griseus produces streptomycin; other species of Streptomyces are responsible for the tetracyclines, such as aureomycin and terramycin. It is interesting to recount that the micro-organisms produce numerous variations on the basis of definite structural patterns and in spite of major differences in the end-products, items that are therapeutically effective, the building stones are relatively simple structures such as amino acid, acetate, and the sugars. Many of the antibiotics produced from bacteria or actinomyces that have been identified are polypeptides derived from amino acids through a different process of biosynthesis than the peptides and protein in animals.

Considerable progress may be recorded also in the understanding of the mechanism of antibiotic action. The pathogenesis of the chemotherapeutic effect varies from one substance to another, with one fundamental action manifest, i. e., the compounds are more toxic to micro-organisms than they are to animal tissues. There is a difference in selective toxicity, while minor changes in the molecule may result in significant change or even loss of therapeutic activity.

The style of cellular processes, nevertheless, is grouped into a limited number of categories, some of which are in process of definition. Considerable progress has been made in understanding the fragile membrane which surrounds the cytoplasm of gram-positive bacteria which is able to withstand a high internal osmotic pressure supported by a rigid cell wall. When certain organisms are exposed to the lysozyme enzyme, the walls dissolve, and the resultant spherical bodies burst when the external osmotic pressure is reduced by dilution with water. When viewed with the electron microscope, they appear as skins that have collapsed. Penicillin and bacitracin interfere with the growth of bacterial cell walls and thereby exert their antibiotic activity. The lack of toxicity for animal cells of penicillin is appreciated because such cells synthesize structures that are chemically unrelated to the substance of the walls of bacteria. Penicillin does not kill or lyse bacteria unless they are growing, and it is not until the cell begins to grow that its existing cell wall fails. A number of antibiotics employed in the practice of medicine are endowed with no lytic action on pathogenic bacteria, and the damage produced is different from that brought about by penicillin. Nor has the microbiological action of

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1. Abraham, E.P.: Antibiotics in Microbiology, Endeavor 18:212, 1959.

streptomycin been elucidated. The broad-spectrum antibiotics, including chloramphenicol and tetracycline, are inhibitors of the synthesis of bacterial proteins.

The understanding of sensitivity and the development of resistance to antibiotics have progressed further in the penicillin-Staphylococcus struggle. The capacity of bacteria to acquire resistance is an example of adaptivity of microbiological life and relates to the basic problems of synthesis of proteins and nucleic acid. A number of bacteria are capable of elaborating the enzyme penicillinase that produces rapid hydrolysis in penicillin. High on the list are rapid strains of staphylococci. These survive; other strains are destroyed. The ability to synthesize the enzyme appears to depend on a specific genetic feature. The enzyme occurs naturally in some organisms; in others its formation can be induced. The rate of synthesis in the second category of bacteria is enhanced by the presence of penicillin.

It is obvious that a great deal of the mystery regarding the origin and chemical structure of the antibiotics has been exposed in recent years.[1] It is inevitable, however, that one hark back to the statement made by Fuller Albright a number of years ago: "A great deal of progress has been made, a great deal of investigation remains for the future."

SCIENCE, WHAT TWISTS THE COMET'S TAIL?

Chicago was fortunate during the holidays in having held within its halls the 126th annual meeting of the American Association for the Advancement of Science. For several days the parent organization, together with 103 of its affiliated societies, revealed such quantities of scientific information—facts, hypotheses, ideas, and opinions—that the intellectual climate of the Midwest can never be the same. About 6,000 scientists came from far and near to hear the communications, to inspect the exhibits, and to ask and answer questions.

Russell Lynes said in the *New York Times* book review section recently that in the last decade 3 billion books of all sorts have been bought by Americans and that "Science indeed scarcely showed its bright face on the best-seller lists at all." A speaker at the recent Chicago meeting estimated that if a person devoted every minute of his time in trying to keep informed of all published material during the year he would still be behind by more than 1.05 billion pages.

In this mountainous output of words, one group of scientists may borrow words from another. Biochemists have borrowed from industry the word "machines," which word was used during the Chicago meeting by a professor of enzyme chemistry when he stated that living systems contain a variety of cellular contrivances or machines which transform energy from one form to another. All known biochemical "machines" have a high degree of ordered structure within which special molecules actually do the energy transforming. The mitochondrion and the chloroplast are the two most fundamental biochemical machines of living systems. They are in effect the power plants of life. The mitochondrion burns sugar (in the form of pyruvic acid) to carbon dioxide and water and converts the energy released by oxidation to the stored energy of adenosine triphosphate (ATP). The chloroplast converts light energy into the bond energy of ATP by an analogous mechanism. Practically all biochemical machines are powered or triggered off by ATP, which in effect stands in the same relationship to cells as does electricity to our homes.

In a communication, "Steroid Hormones and Aging in Man," it was noted that the principal adrenal cortex hormone, hydrocortisone, and its metabolites are excreted in about the same amount in young as in elderly men and women. However, numerous studies have shown that, after the age of 20 years, a significant and steady decline in output of the 11-deoxy-17-ketosteroids occurs and that their relative deficit in aged persons may be responsible for such phenomena as weight loss, muscle wastage, and weakness.

Another speaker in the symposium on aging stated that the downward trend of employment of persons over 65 years of age continues and that today only one-third of all men and one-tenth of all women over 65 years of age are regularly employed. The median income of these employed older workers is $3,475 annually. But despite the weighting of these earnings, 40% of all older couples and 60% of all older single persons have incomes below minimum standards. The speaker suggested that a competent, high-level commission should be called together to advise government and industry on adequate, dependable, and coordinated methods of meeting the economic needs of older people.

A study of guests in an old people's home revealed that a wide variety of physiological functions show an apparent linear decrease between the ages of 30 and 90 years, the average varying widely for different functions tested under resting conditions. The rate of conduction of impulses in the ulnar nerve, for example, diminishes by 15% at the age of 30 years, whereas the blood flow through the kidney is reduced by 50% and the resting cardiac output by 30%. Studies of various renal functions indicated that with advancing age nephrons are lost as functioning units. Many other organ systems also showed varying degrees of functional impairment.

In this symposium on aging stress was defined, for practical purposes, as the consequence of the rate of "wear and tear" in a biological system, which system may be the organism as a whole (systemic stress) or one of its parts (topical stress). The visible manifestations of the former constitute the "general adaptation syndrome" while those of the latter are known as the "local adaptation syndrome." Both of these are triphasic reactions which evolve through an acute phase, the "alarm reaction," to the "stage of resistance" and finally end in the "stage of exhaustion." Stress is a general manifestation of any kind of vital activity (heartbeat, respiration, glandular secretion, or locomotion) which produces some "wear and tear." Hence, stress is not necessarily a pathological phenomenon, and complete freedom from it never occurs in living beings.

Among the exhibits at the Chicago meeting was a display of music and records of the space age intended to interest youngsters 6 years of age and older and give them some understanding of fundamentals. This was referred to as the "beep beep" school, and the six best-sellers among the records were "Constellation Jig," "Planet Minuet," "Ballad of Sir Isaac Newton," and "It's a Scientific Fact."

The president of the National Science Teachers Association believes that children in elementary schools today know much more science than we give them credit for and that they can learn throughout school much more science than we give them an opportunity to learn. Youngsters talented in science, he said, can be identified by the end of the sixth grade if science is well integrated into the curriculum for young children.

The retiring president of the AAAS, in his address at an evening session, said that by the overlapping expansion and growth of this nation's science programs a crisis has come about whereby none of the major programs can be adequately supported except at the expense of less glamorous areas of science, education, and culture. Even when stimulating conditions have been removed, the top priority label is often maintained; then another set of circumstances dictates the creation of another top priority label assignment to another area of science. He suggested "a liaison of government scientists with academic and industry scientists, to be represented by a national science council, in a manner compatible with the maintenance of our broad culture and balanced development."

A professor reported on a group of employed men beyond the age of 64 years, some of whom had retired and some of whom continued to work. The study was continued for several years, and, contrary to popular belief, no evidence was found that retirement affects health. The relation between the retirement and the death of a person a few months later was explained largely by the fact that persons in poor health tend to retire. On the other hand some evidence was found that retirement actually improved the health of some people. The speaker recommended that a person be permitted to work as long as he wants to do so and can measure up to an objective standard of accomplishment.

In a symposium on unsolved problems in biology, a professor of zoology described two classes of hereditary behavior. In most situations, he said, the parents make equal contributions to the traits of their offspring, and the numerical relations between the traits of the parents and those of the offspring are described fully by the classic Mendelian laws and their more recent extensions. Such heredity is governed by the behavior of the chromosomes in the nucleus of the cell. The other class of hereditary behavior is a conspicuous exception to the Mendelian rules. Instead of both parents, only the mother determines a particular trait in her offspring, and since this type of inheritance seems to be unrelated to the cell nucleus, it is assumed to be controlled by the cytoplasm, most of which, if not all, the mother contributes to the offspring. Such inheritance is called maternal or cytoplasmic inheritance. The existence of these two classes of hereditary behavior raises a fundamental question in genetics. If DNA, or a similar chemical compound, can be found in the cytoplasm specifically associated with the traits, we may be able to conclude that no fundamental difference exists between the two types of inheritance. However, if no relation can be established between DNA and cytoplasmically controlled traits, we must conclude that hereditary information can be stored and transmitted in other ways. Several possibilities concerning the supplementary mechanisms of storage can be suggested, but the facts required for a full interpretation are not yet available.

Studies in recent years have revealed that cytolysis is not restricted to human cancer cells and to human serums but that it can be reproduced in experimental ascites tumor cells and by various animal serums. At this meeting a group of investigators reported on experiments, mainly in vitro, on the possibility of cytolysis of tumor cells under the influence of soaps. Different ascites tumor cells and such non-neoplastic cells as erythrocytes, mammalian liver cells, and thymus lymphocytes were studied with respect to their sensitivity to cytolysis by the sodium salts of different saturated monobasic fatty acids. The investigators reported that fatty acids with a chain shorter than nine carbons do not destroy the mammalian liver cells and erythrocytes but attain a cytolytic effect on strongly proliferating cells, such as thymus lymphocytes and malignant cells. The strong cytolytic potency of the high molecular fatty acids is caused by the higher predominance of their nonpolar lipophilic part.

A mathematician, an automation expert, delivered an address entitled "The Nature of Social Dangers of the Controlled Machines of the Future." Obviously he talked about a different kind of "machine" from that mentioned in a previous paragraph. It is erroneous to assume, he said, that machines cannot possess any degree of originality. On the basis of such an assumption, many people pooh-pooh the dangers of thinking machine techniques, one of which is that they are able to act so quickly. Even when they do not transcend human intelligence in any way, they very well may, and do, transcend men in the performance of their tasks. By the very slowness of human activities, our effective control of our machines may be nullified. If such machines become more and more efficient and operate at a higher psychological level, the dominance of the machine becomes nearer and nearer.

An astronomer reported that radio signals picked up from the planet Jupiter in recent months indicate the presence of a magnetic field in space about 100 times stronger than the well known Van Allen belt around the earth. He also reported that the radiotelescope provides information indicating that the surface temperature on the planet Venus is about 585 degrees F. It is unlikely that liquid water exists anywhere on the surface of Venus. It is unlikely also that life exists on this planet.

Two university scientists, one a physicist and the other an astronomer, expressed opposing opinions about the forces that twist a comet's tail. The physicist theorized that a ring of flaming gas surrounding the sun generates a solar wind because of its 2 million degree heat and that the solar wind strikes the comet's tail and deflects it. Since comet tails contain little mass, comparatively small forces would be required to change their angle to the comet heads. The astronomer maintained that only small quantities of gas leak from the surface of the sun, except in case of great disturbances like solar flares, and that large quantities of gas (the solar wind) would be prevented by the sun's magnetic field from escaping from the sun.

From the best of vantage points, one could noc wholly scan the tremendous annual output from so many scientific societies. However, from a restricted view of a few programs one can safely say (1) that scientists today hold diverging opinions on many important problems and that only continuous intensive study will reduce the number (young people who contemplate scientific careers, therefore, should have no fear of having new worlds to conquer) and (2) that the electron microscope has so broadened and deepened what formerly could not be observed as to amount to a revolution in the biological sciences.

As we enter the space age the number of unsolved problems in science will increase. There will be many problems that need more immediate attention, with possible practical results, but there will be few in outer space of more interest to everyone than that of finding out what twists the comet's tail.

DESERT MEDICINE

The practice of medicine 50 years ago in the rugged, sparsely settled desert of the Southwest has been described vividly by one who was there.[1] Joseph H. Peck migrated to western Utah after graduation from Ensworth Medical College, St. Joseph, Mo. He plied his skill in a desolate land under as extenuating and primitive conditions as demanded in any area of the United States. The Western Pacific Railroad had been completed between Salt Lake City and California some years earlier. A spur was being laid south from Westover on the Utah-Nevada state line. This bordered the Great Salt Lake Desert to service a newly developed copper mining area in the Deep Creek Mountains. The Bonneville Salt flats were nearby. These flats, which have become famous in recent years as a speedway, are completely incapable of supporting flora or fauna.

The practice of medicine in the early days in this frontier land should be described and documented by those who can tell the story from firsthand experience i:: as delightful a style as Doctor Peck. A considerable revival of interest in preserving much of the "Old West," particularly of politics, mining, and railroading, may be recorded in recent years, quite unrelated to adult westerns. Medicine has received less than its proportionate share of interest during the recreation of communities such as Virginia City, Nevada, Ouray, and Leadville, Colo., and the failure to abandon the last spur of narrow gauge railroad that originates in Durango, Colo. These are four historical items that have as much to command attention as the Strip in Las Vegas, an example of a 1960 frontier community, or Monticello, Utah, a center for those on the quest of uranium deposits.

Two incidents in the small volume on Peck reflect the change in living over the years. The imposition of quarantine of a home stricken with scarlet fever will be recalled by the physicians who began practice before World War I. At that time no one except the physician was allowed to enter the quarantined home. Everything that was allowed to cross the threshold was either eaten, burned, or fumigated with sulphur candles before the quarantine was lifted. Another narrative concerned Eddie Rickenbacker, a many-faceted pioneer in American transportation on land and in the air. As a young man, Mr. Rickenbacker held several international automobile records prior to joining the Lafayette Escadril in World War I. On one occasion he became mired in the mud and sand in western Utah while attempting to establish a new transcontinental record by automobile. The extraction of the racing car is delightfully told by the author.

The author of "What Next" began his career of writing, at the age of 60 years, after retirement from medical practice. This latest effort is a notable contribution to documentation of frontier days in the great southwestern desert, a formidable barrier for most of the overland migration prior to the completion of the transcontinental railroad. Dr. Peck's efforts may serve as an incentive to other physicians who have experiences to relate and whose capacity to tell a story should be exploited. It is hoped that the number of medical novelists will be expanded and be productive before the experiences are lost forever.

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1. Peck, J. H.: What Next, Doctor Peck? Englewood Cliffs, N. J., Prentice-Hall, 1959.

DEPARTMENT OF INVESTIGATION

NEW CELLS FOR OLD

FOR "WELL-HEELED" OLDSTERS

Popular magazines recently have published many articles on the subject of health and disease. Occasionally the editors of certain magazines publicize an unestablished remedy, which brings it to the attention of the public as a medical discovery of alleged value in one or more disease categories.

Such an item has appeared in *Coronet*, a popular pocket-sized magazine; it covered the methods and claims of Dr. Paul Niehans, a Swiss physician. The editors noted that "Cellular therapy is a startling European treatment for old age and a wide variety of diseases. Because this medical technique is controversial and still unproven, *Coronet* asked Dr. Herbert S. Benjamin, an American physician and medical researcher, to discuss it with its discoverer, Dr. Paul Niehans of Switzerland, and to observe his work and evaluate the use of cellular therapy by many physicians in Western Europe . . ."

Dr. Paul Niehans has had the benefit of other items of publicity written on his behalf. The greatest flurry of such press-agentry occurred when he was called to treat the late Pope Pius XII in February, 1954. Among others who are alleged to have received his attention are Konrad Adenauer and W. Somerset Maugham.

The late Pope was suffering from a gastric disorder, the exact nature of which was never clearly described but which apparently involved a distressing bout with hiccoughs. The late Holy Father had at least one other physician in attendance, one Professor Galeazzi-Lisi, who later became involved with the Italian medical fraternity by selling photographs and an account of the late Pope's dying hours.

There is no clear indication, either, in all of the publicity which attended the nonfatal papal illness, whether or not fresh cell therapy, or royal jelly (another publicized rejuvenator), or the passage of time was responsible for his recovery. The Chicago *Tribune*, however, on June 3, 1957, in an Associated Press release bearing a Rome date line, reported that Dr. Niehans had written a book entitled "Niehans, Doctor of the Pope." Niehans was described in that news dispatch as having credited potato soup with being the effective therapeutic agent.

Beyond other newspaper publicity, Dr. Niehans has had the benefit of several magazine articles. A magazine called *Top Secret*, which was not dated, but was purchased in August, 1954, had an item entitled "Modern Miracle in the Vatican: The Controversial Doctor Who Saved the Pope's Life!" For some reason, however, this item did not reveal the use of potato soup. This account of the treatment was as follows:

> In February 1954, the world was confronted with a miracle in the great tradition of the Church. But it was a modern miracle in which twentieth century science cooperated with religion. In the recovery of the saintly Pontiff, his own abiding faith was aided by the skill of a physician who is a mystery man among the great doctors of the world. *Top Secret* can now reveal exclusively that the Pope's life, at what seemed to be the eleventh hour, was saved by the intervention of a 72-year-old Swiss physician named Dr. Paul Niehans. . . .
>
> Dr. Niehans is a controversial figure in the world of international medicine. He is a surgeon and, in five decades of practice, has performed thousands of operations and written twenty books on surgery. Yet surgery is his last resort. . . .
>
> Niehans then applied to the Pope his own special methods of treatment, known as cellular therapy. This unorthodox method consists in the transplantation of living cells from a freshly slaughtered animal.
>
> And in conjunction with this, a new miracle drug called "xylocaina," used to alleviate pain resulting from abdominal surgery, was given to the Pope. This drug was developed by Dr. Niehans in his own laboratories in Switzerland. . . ."

The Dec. 10, 1957, issue of *Look* magazine carried an item entitled "Is This Man Keeping the Pope Alive?" Reference was made to the use of cell therapy.

Mention of Dr. Niehans has also been made in *Time*. The Sept. 13, 1954, issue, in an item entitled "Help From Animal Cells?", referred to the use of glands and organs of animals being utilized by Dr. Niehans as long ago as 1931 and reported his reading of a paper before some physicians in Karlsruhe, Germany. This item included the following statement.

> Several doctors who have adopted the Niehans technique, giving injections of embryonic animal cells at costs ranging from $3.50 to $20, supported his claims. But others shook their heads. There are great dangers: allergic reactions, shock, accidental infection with viruses or other microbes. There is a good chance that the "placebo effect" (i. e., mental suggestion) is responsible for improvement in many patients.

Another issue of the same publication (*Time*, Aug. 31, 1959) contained an item concerning Dr. Niehans, entitled "The Healing Lamb."

The 1954 publicity prompted an inquiry from the Department of Investigation to the Swiss Medical Institutions at Bern. Following is the response received from the secretary:

> Dr. Paul Niehans, domiciliated at Clarens, uses to make injections of fresh organ's pap, to what he attributes an effect on the corresponding organ. This way of treatment is

> at the utmost specialized, as he injects, for instance, a substance of the interbrain against insomnia. The idea is at least 100 years old and the treatment with organ's dialysates has been tried several times. However, a sound scientific basis is not yet established. In Switzerland, Dr. Niehans did not succeed in gaining a great number of adepts, but it seems that this is more the case abroad.

Of interest, also, are the items critical of Niehans and his method. THE JOURNAL, (156:1348 [Dec. 4] 1954) under the heading Foreign Letters, carried an account of some untoward effects, including brucellosis and encephalomyelitis, developing in some patients treated with "fresh cells." This was described as having been reported by Professor Bennhold of the University of Tuebingen Medical School.

The European medical literature contains several references to the use of fresh cell therapy. One of these, entitled "Historical Development of Fresh Cell Therapy and its Application in General Practice", was published in the *München. med. Wchnschr.* for May 27, 1955 (Vol. 97, pp. 698-703). This discussed methods of administration, and suggested that the patient should be sleeping and should not awaken for at least 24 hours.

Another report, entitled "Fresh Cell Therapy: Critical Evaluation of Theory and the Nature of the Fresh Cell Therapy According to Niehans", by A. Pischinger, was published in the *Wiener medizinische Wochenschrift* (105:952-957 [Nov. 19] 1955). In this article Pischinger criticizes the Abderhalden serum test, which apparently is used by Niehans for diagnostic purposes. In addition to recalling harmful effects from the injection of fresh cells, including infections, it is stated that death has been traced to the treatment. This author questions the Niehans claim that fresh cell therapy is organ-specific, recounting his experience with animal experimentation, that no matter what organ source was injected, the biological effect was the same immediately after the injection.

Another critical report, entitled "Possibilities and Limitations of Cell Therapy," was published in the *Münchener medizinische Wochenschrift* (97:703-707 [May 27] 1959). The author, H. G. Rietschel, outlines three phases involved in cell therapy, the first being described as a hormone effect, the second as the stress stage (between the 11th and 14th day), and the last, one of regeneration. He points out that the likelihood is that cell therapy acts on the general cell metabolism but that specific effects, in the sense of a regenerative stimulation of a certain organ, have not been observed clinically.

There is reference to a patent granted in Switzerland in October, 1952, to Leo Schwander and Paul Niehans. This is a process of preservation of organ-cell preparations by freezing and sublimation. There is also a firm called Rhein-Chemie, Abteilung Dr. Niehans, in Heidelberg. In a promotional booklet called "Dr. Niehans Zellular-Therapie, Siccazell . . .", which, among other things, warns that cellular therapy is not a panacea and is contraindicated in all inflammatory diseases and in focal toxicoses, it is stated that there are certain diseases wherein the method is not successful. These include "amyotrophic lateral sclerosis, chondrodystrophy, lymphogranuloma, morbus Bechterew, Paget's disease, multiple sclerosis, myasthenia gravis pseudoparalytica, myatonia congenita, Parkinson's disease, postencephalitic conditions, scleroderma, syringomyeloma and all forms of leukemia."

The product is recommended in heart diseases, circulatory disturbances, arteriosclerotic changes and hypertension, climacteric, sterility, impotence, arthritis and rheumatism, mongolism, and prostatic diseases (including adenoma of the prostate). In the circumstances, such claims cannot be regarded as established. An attitude of scientific "Missourianism" will undoubtedly prevail in this country.

From European discussions and observations it is fair to say that the most favorable impression of the cell therapy is that it is experimental at best and does not provide, in the hands of others, what the originator claims for it. To an observer of some skepticism, however, this method of promotion brings a typical reaction, i. e., having failed to impress critical medical observers, the possessors of the particular treatment resort to the familiar methods designed to create a demand for a medical commodity.

On the other hand, THE JOURNAL (165:2133 [Dec. 21] 1957) carried an abstract of a report by G. Destunis entitled "The Treatment of Mental Deficiency and Encephalopathies in Childhood by Means of Fresh Tissue and Siccacell." This was from the *Archives of Pediatrics* and reported in part:

> In diencephalon implantations, a section of calf brain comprising the whole diencephalon and weighing approximately 20 Gm. is comminuted, and stirred into a mash to which is added 100,000 to 200,000 units of penicillin, and injected under pressure through a wide-bore cannula into the gluteal region of the patient. . . .
>
> Revitalization follows diencephalon implantation. The children are more alert, fresh, and balanced; they have better appetites and a more restful sleep. They take a more active part in the daily life of the family and show more interest in their schoolwork. Their intelligence, memory, and capacity for giving attention are advanced by some 6 to 12 months.

Beyond the latest item of Niehans' publicity in *Coronet* for December, 1959, written by Herbert S. Benjamin, M.D., there was an item in a gossip column in the Chicago *American* for Nov. 24, 1959, as follows:

> Gilles Lambert, author of "The Conquest of Age," is being kept under wraps by his publishers because so many people are trying to get to him. His book is the story of the fantastic rejuvenating methods used by Swiss Dr. Niehans, and Lambert is swamped with letters, phone calls and telegrams from would-be patients. Usually the doctor accepts only celebrities. Treatments are $500 each.

MEDICAL NEWS

CALIFORNIA

Harvard Alumni Meeting.—There will be a meeting of the Harvard Medical Alumni Association of Southern California at the California Club, 538 S. Flower St., Los Angeles, at 6:30 p. m., Friday, March 11. Dr. Rolf Lium, Portsmouth, N. H., president of Harvard Medical Alumni Association will be guest speaker. Harvard Medical Alumni wishing to attend this meeting should secure information from Dr. Lowell F. Bushnell, 1321 Vermont Ave., Los Angeles 27.

Personal.—Dr. Edward P. Luongo, Los Angeles, was appointed regional medical director for the West Coast of the Mobil Oil Company. Dr. Luongo had been medical director of General Petroleum Corporation since 1947. General Petroleum became a part of Mobil Oil Company on Jan. 1. Dr. Luongo is a diplomate and founder of the American Board of Occupational Medicine.——Dr. Anthony A. Mira, Forest Hills, N. Y., was appointed medical director of the General Telephone Company of California in Santa Monica. Dr. Mira had been medical director of the New York City Department of Welfare from 1945 to 1954. Since 1957 he has been director of the Bureau of Industrial Health and Workmen's Compensation of the Medical Society of the State of New York.

Health Team Begins African Program.—Mr. Karl Fischer, sanitarian and health educator at the College of Medical Evangelists, flew to Dar es Salaam, capital and principal port city of Tanganyika, East Africa, Jan. 18 to launch a new research and preventive medicine program. He will travel by train and bus some 800 miles inland to his destination near the northern end of Lake Tanganyika. Mr. Fischer will be the first of a team of health and medical specialists who will later locate at Heri Hospital, field headquarters for the program. The Research and Assistance Program, as the project is called, dates back to 1956 when six CME scientists made a comprehensive medical survey of East Africa. This survey was continued during the summer of 1957. In the latter part of 1957 the scientists recommended that CME undertake a four-year research and preventive medicine program. Dr. Harold N. Mozar, Loma Linda, director of the CME School of Tropical and Preventive Medicine, which is heading the program, explained that the purpose of the program "is to give medical assistance with emphasis on health education and preventive medicine. A continuous research effort will be aimed at gathering information about local tropical diseases and their causes." Mr. Fischer will direct construction of living quarters and a health education center and research building for other members of the project when they arrive later. After this initial construction is finished, the first group of 12 Africans will arrive and the first three subjects—housing, sanitation, and agriculture—will begin. Members of this first group are teachers from East Africa. They with their families will come to Heri and live for a period of 18 months. Heri Hospital is 40 miles south of Kogoma, a town at the northern tip of Lake Tanganyika.

CONNECTICUT

Yale Celebrates Sesquicentennial.—The Yale School of Medicine, New Haven, will celebrate a century and a half of existence on Oct. 28-29 of this year. The occasion will be marked by meetings, exhibitions, and addresses. Among the guest speakers will be Sir Howard Florey, of Oxford, England. It was in October, 1810, that the Connecticut General Assembly granted a charter to Yale College for the establishment of the Medical Institution of Yale College and the first medical school in the United States came into being. The first medical faculty at Yale included Eli Ives and Jonathan Knight, who became presidents of the American Medical Association. From the start the Connecticut Medical Society was a partner in the enterprise and worked in close cooperation during the first half century of the school's existence. Other events associated with the sesquicentennial celebration will take place during the academic year 1960-1961. These include an exhibition of medical art at the Yale Art Museum and a scientific meeting to be held in conjunction with the dedication of a new medical school auditorium.

ILLINOIS

Hospital News.—The medical staff at Little Company of Mary Hospital, Evergreen Park, elected the following officers for the 1960 year: Dr. James W. West, president; Dr. Stanley E. Ruzich, president-elect; and Dr. John J. Brosnan, vice-president. Other officers of the staff include Dr. James B. O'Neill, secretary, and Dr. Raymond P. Murphy, permanent treasurer, of Chicago.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Chicago

Annual Lecture.—The 1960 annual D. J. Davis Memorial Lecture on Medical History will be given at 1 p. m., Wednesday, March 3, in Room 221 of the Dental-Medical-Pharmacy Building of the University of Illinois, 1853 W. Polk St. The lecturer will be Barry J. Anson, Ph.D., chairman and Robert Laughlin Rea Professor of the department of anatomy, Northwestern University Medical School. His subject will be "Mediaevel Medicine: Pre-Christian Fabric and Present-Day Remnants."

Annual Clinical Conference.—The Chicago Medical Society will hold its 1960 annual clinical conference at the Palmer House March 1-4. The program lists the following out-of-state participants:

Drs. Michael E. DeBakey, Houston, Texas; John Beach Hazard and Eugene F. Poutasse, Cleveland; John I. Nurnberger, Indianapolis; Howard P. House and Morton D. Leigh, Los Angeles; Thomas E. Machella, Philadelphia; Raymond J. Jackman, Oscar T. Clagett, William G. Sauer, and Louis A. Brunsting, Rochester, Minn.; Robert J. Coffey, Washington, D. C.; Edward H. Kass, Leo P. Krall, and Edward A. Gaensler, Boston; Sol Sherry and Willard M. Allen, St. Louis; Thomas H. Holmes III and Clement A. Finch, Seattle; William H. Zinkham, Baltimore; Horace H. Zinneman, Minneapolis; Rulon W. Rawson, New York City; H. William Clatworthy Jr., Columbus, Ohio; and Richard H. Egdahl, Richmond, Va.

Panel discussions are planned on control of the spread of cancer and reactions to drugs. A clinical pathological conference will be held the afternoon of March 1. Film lectures will be held each morning and television programs will be presented each afternoon. Instructional courses and scientific exhibits are planned. A ladies' program is arranged. Registration fee for nonmembers is $10. For information, write the Chicago Medical Society, 86 E. Randolph St., Chicago 1.

Meeting on Medical History.—There will be a meeting of the Society of Medical History of Chicago at the Institute of Medicine (Fourth Floor, 86 E. Randolph St.) on Wednesday, Feb. 17, 8 p. m. This is an open meeting; all are welcome. The program will be as follows:

Dr. Morris Fishbein, editor, *Excerpta Medica*, "Evolution of Quackery."

Dr. Frederick Stenn, assistant professor of medicine, Northwestern University Medical School, "The Historic Importance of the McCormick Institute for Infectious Diseases."

For information, write Dr. Leo M. Zimmerman, 55 E. Washington St., Chicago 2, secretary.

Hospital Builds Research Building.—Presbyterian-St. Luke's Hospital has received a one-million-dollar gift from John F. Jelke Jr., retired Chicago manufacturer. The gift will be used by the hospital toward the construction of its new medical science research building which presently is under construction. The building, named the Jelke Memorial Building, eventually will consist of 15 floors. The lower floors will be devoted to laboratories, operating suites, observation galleries, and seminar class rooms, and upper floors devoted to bed-patient areas. The gift will enable the hospital to proceed with the completion of the presently planned portion of the ultimate building.

INDIANA

Society News.—At its annual business meeting on Dec. 13, the Indiana Association of Pathologists elected the following officers: Dr. John D. Stepleton, Richmond, president-elect; Dr. Anthony Pizzo, Bloomington, board member; Dr. Leon L. Blum, Terre Haute, installed as president; Dr. Lester H. Hoyt, Indianapolis, reelected councilor; and Dr. David L. Adler, Columbus, assemblyman.——The officers of the Indiana Roentgen Society, Inc., are: president, Dr. John R. Lionberger, South Bend; president-elect, Dr. Chester A. Stayton Jr., Indianapolis; and secretary-treasurer, Dr. David E. Wheeler, 1500 N. Ritter, Indianapolis, Ind. Meetings are held twice a year; the first Sunday in May and during the fall meeting of the Indiana State Medical Association.

Personal.—The Evansville Board of Health on Dec. 16 appointed Dr. Arnold W. Brockmole as director of the City-County Health Department to succeed Dr. Minor Miller, who died in November. Dr. Brockmole, former assistant to Dr. Miller, left Evansville early last year to head the health department in Butte County, Calif.——Dr. Dorothy L. Carter, a native of England, has joined Miles Products, Division of Miles Laboratories, Inc., Elkhart, as research and medical director. Dr. Carter's responsibilities include the administration of all research and medical activities pertaining to the Miles Products division and the coordination of the division's research and medical policy with that of the parent company.

KENTUCKY

Dr. Glass Honored.—On Dec. 13 citizens of Henderson honored Dr. James G. Glass, Henderson, "for 50 years of dedicated medical service to mankind." The physician was honored in a special ceremony at the First Baptist Church. Meharry Medical College, his alma mater, recently presented Dr. Glass with the "President's Award" for 50 years of service —1908-1958.

MASSACHUSETTS

Fund for Research in Ophthalmology.—Establishment of the Max, Martha and Alfred M. Stern Fund at Harvard University, Boston, for research in ophthalmology "and for studies regarding glaucoma and cataract . . . or closely related to the diseases of the eye" was announced by Dr. George P. Berry, dean of the faculty of medicine. The gift of $125,000 was made to the university under the terms of a living trust created by the late Mrs. Martha Stern, of Cincinnati, widow of Mr. Max Stern and mother of the later Alfred M. Stern, Harvard alumnus. Under the terms of the gift extension of the studies into broader fields of ophthalmology may be made in the future "if it is thought that such extension would fruitfully add to knowledge about the eye and its diseases." The studies are carried on in the Howe Laboratory of Ophthalmology of the Harvard Medical School and the Massachusetts Eye and Ear Infirmary.

University News.—An International House for single and married foreign and American students and their families will be developed by the Harvard School of Public Health on Park Drive in Boston's Fenway area following the purchase of three apartment buildings. A committee sponsoring an effort to raise funds to finance renovations of the three buildings is organized. Present plans include provision for 70 living units, common rooms, library, and a recreation area as well as redecorating and furnishing throughout.——Manfred L. Karnovsky, Ph.D., associate professor, was named acting head of the department of biological chemistry in the Harvard Medical School, Boston, He fills a vacancy created through the resignation of Eric G. Ball, Ph.D., who served as acting head of the department since December, 1958, and who requested to be relieved of his duties because of his responsibilities as chairman of the division of medical sciences and his teaching and research.

MISSOURI

Physicians Meeting in Columbia.—The American College of Physicians will hold its Missouri regional meeting Saturday, Feb. 20, at the auditorium of the University of Missouri School of Medicine, Columbia. Dr. Wesley W. Spink, Minneapolis, vice-president of the college, will speak at the luncheon at the Missouri Student Union Building. The program includes 13 papers plus 11 papers to be read by title. A symposium on active immunization will be opened by Dr. Spink. A social hour and dinner will be held at the Daniel Boone Hotel beginning 6:30 p. m. Dr. Paul O. Hagemann, St. Louis, is governor of the college for Missouri. For information, write the American College of Physicians, 4200 Pine St., Philadelphia 4.

NEW YORK

Seminar on Advances in Rehabilitation.—The American Academy of Physical Medicine and Rehabilitation, the State University of New York Downstate Medical Center, and the Kings County Chapter, American Academy of General Practice will sponsor a seminar, "Recent Advances in Rehabilitation Medicine," Friday and Saturday, April 15 and 16, at the Downstate Medical Center, 450 Clarkson Ave., Brooklyn 3. The seminar is supported by a grant from the American Rehabilitation Foundation. A. A. G. P. registrants are entitled to 12 hours of category I credit. For information, write the Downstate Medical Center at the above address.

Fraternity Lecture.—Allen O. Gamble, Ph.D., manpower evaluation and development officer for the National Aeronautics and Space Administration, gave the Alpha Omega Alpha Lecture at Albany Medical College, Jan. 28. His lecture was entitled "Testing, Selection and Training of Astronauts." Dr. Gamble was named to his present post in November, 1958. NASA is a 10,000-man federal research and development agency charged with the responsibility for the nation's civilian space exploration and aeronautical research. Dr. Gamble is in charge of the agency's examining, selection, college recruiting, training, and graduate education programs.

Society News.—The New York Proctologic Society elected the following 1960 officers: president, Dr. Saul Schapiro, Brooklyn; vice-president, Dr. Maus W. Sterns Jr., New York City; and secretary-treasurer, Dr. Norman L. Freund, Brooklyn.——Dr. William A. Brumfield Jr., White Plains, Westchester County health commissioner was elected president of Annual Health Conference Inc., a nonprofit organization chartered by the Secretary of State which sponsors the Annual Health Conference. Other sponsors are the New York State Health Department, the New York State Public Health Association, the Association of School Physicians and School Nurse-Teachers and New York State Health Officers Association. Other officers elected are Dr. Thomas E. Snyder, East Syracuse, vice-president; Dr. Granville W. Larimere, Albany, secretary; Dr. James J. Quinlivan, Albany, assistant secretary; and Marion L. Henry, Delmar, treasurer. The 56th Annual Health Conference will be held May 23-26 in New York City.

New York City

Dr. Goldberger Honored.—Dr. Isidore H. Goldberger, director of health education emeritus of the Board of Education of the City of New York, and clinical professor of pediatrics at New York University School of Medicine, was the guest of honor at the 13th anniversary dinner tendered by the medical board of the Morrisania City Hospital, of which he was a founder, on Saturday, Dec. 19.

Annual Lecture.—The department of dermatology and syphilology, New York University Post-Graduate Medical School, announced that the third annual Howard Fox Memorial Lecture will be delivered by Dr. Robert A. Nelson Jr. on Tuesday, Feb. 16, 8 p. m., in Classroom B of Alumni Hall, 550 First Ave. Dr. Nelson is senior investigator, Howard Hughes Medical Institute, and research professor of medicine, University of Miami School of Medicine, Gainesville, Fla. The title of his talk will be "Immunologic Mechanisms of Resistance to Microbial Infection and to Transplantation of Homologous Tissues."

New Professorship in Cardiovascular Disease.—A new research professorship in cardiovascular disease was established at the Columbia University College of Physicians and Surgeons. The chair, called the Westchester Heart Association Professorship of Cardiovascular Research, is supported partially by a grant from the Westchester Heart Association, Inc. Dr. Andre F. Cournand, professor of medicine at Columbia and a joint winner of the 1956 Nobel Prize in Medicine, has been named first incumbent of the new professorship. Dr. Cournand has been at Columbia since 1930 and has been director of the Cardio-Pulmonary Laboratory Division for 15 years. The Westchester Heart Association, a chapter of the American Heart Association, was founded in 1950 by a group of Westchester County doctors. The chapter operates the Cardio-Respiratory Laboratory at Grasslands Hospital in Valhalla, N. Y.

Personal.—Dr. Griffith J. Winthrop was appointed assistant medical director at E. R. Squibb & Sons. Dr. Winthrop until recently was in private practice in Canandaigua, N. Y.——Dr. Theodore G. Klumpp, president of Winthrop Loboratories, was elected to the board of directors of Sterling Drug Inc. Winthrop Laboratories is Sterling's major pharmaceutical division. Dr. Klumpp had been chief of the Drug Division, U. S. Food and Drug Administration, and director of drugs, food and physical therapy and secretary of the council on pharmacy and chemistry, American Medical Association.——Dr. Harry Lane Robinson, assistant clinical professor at New York University's College of Dentistry for the past two years, was named professor and chairman of the department of pathology. Dr. Robinson is an attending pathologist at the Veterans Administration Hospital, and an attending surgeon at Mother Cabrini Hospital, Manhattan.

OHIO

Annual Lectures in Cincinnati.—On Saturday and Sunday, April 9 and 10, Dr. John W. Hope, director, department of radiology, Children's Hospital of Philadelphia, will deliver the 12th annual Joseph and Samuel Freedman Lectures in Diagnostic Radiology at the University of Cincinnati College of Medicine. There will be no charge for the lectures. Radiologists desiring to attend are requested to write Dr. Benjamin Felson, X-Ray Department, Cincinnati General Hospital.

VIRGINIA

Regional Meeting of Physicians.—The American College of Physicians will hold a regional meeting for Virginia Saturday, Feb. 20, at the Medical School Amphitheatre of the University of Virginia, Charlottesville. The following papers include invited authors:

Use of Antibiotics, Dr. Calvin M. Kunin, Boston.
The Pathogenesis of Glomerulonephritis, Drs. Alvin E. Parrish, Norman C. Kramer, Fred E. Hatch, Mary F. Watt, John S. Howe, Washington, D. C.
The Role of Alveolar Machrophage in Resistance to Tuberculosis, Quentin N. Myrvik, Ph.D.
Cerebral Vascular Disease, Dr. Fritz E. Dreifuss, Charlottesville.
A Re-evaluation of the Hemodynamic Changes in Cirrhosis of the Liver, Dr. W. Dean Warren, Charlottesville.
Pathophysiology of Hyperbilirubinemic States, Dr. Aubrey Brown, Charlottesville.

Dr. Chester K. Jones, Boston, regent of the college, will present an address at the evening dinner session. Governor of the college for Virginia is Dr. Kinloch Nelson, Richmond. For information, write the American College of Physicians, 4200 Pine St., Philadelphia 4.

WEST VIRGINIA

Ease Requirements for Foreign Physicians.—The West Virginia Medical Licensing Board has liberalized the requirements for service by foreign educated physicians in state institutions. This action was taken at the winter meeting of the board held in Charleston on Jan. 11. Governor Cecil H. Underwood proposed that legislation be enacted governing the employment of foreign trained physicians in the state institutions. The effect of the board's decision will permit foreign trained physicians to practice in state hospitals and institutions for a period of one year with the understanding that permits issued may be renewed indefinitely. Temporary authorizations for foreign graduates entering West Virginia for internships or residencies will be granted providing such graduates fulfill all the requirements of the board as stipulated in the regulations, and provided that they agree to appear in person at the next meeting of the Medical Licensing Board. The revised regulations require all foreign graduates to submit their medical credentials to the board for evaluation by the proper agencies. Such graduates serving in state institutions will be required to take the regular licensing examination as soon as they become eligible. Before the regulations were revised, graduates of foreign medical schools were permitted to work, under supervision, as residents and interns in hospitals not more than four years.

GENERAL

Psychoanalytic Association Changes Address.—The American Psychoanalytic Association announced the change of address of its central office, effective Dec. 15 to One East 57th St., New York 22 (fifteenth floor); Telephone: PLaza 2-0450.

Surgical Meeting in Hawaii.—The eighth congress of the Pan-Pacific Surgical Association will be held Sept. 27-Oct. 5 in Honolulu, Hawaii. All members of the medical profession are eligible to register. Ten surgical specialty sections will be held simultaneously. Information and brochures may be obtained by writing Dr. Forrest J. Pinkerton, Director General, Suite 230, Alexander Young Building, Honolulu 13, Hawaii.

Three Researchers Receive Award.—The first-place 1959 Glycerine Research Award of the Association of American Soap and Glycerine Producers, Inc., was awarded to Dr. Stanley W. Jacob, assistant professor of surgery, University of Oregon Medical School, Portland; Dr. Ernest M. Barsamian, of Harvard Medical School, Boston; and Samuel C. Collins, Ph.D., of the Massachusetts Institute of Technology. The prize-winning research project involved the successful transplantation of puppy hearts, which had been dehydrated and supercooled, using glycerine as an "anti-freeze." The work was done under the auspices of Harvard and MIT.

Congress on Gerontology in San Francisco.—The International Association of Gerontology will meet in San Francisco, for its fifth International Congress of Gerontology, Aug. 7-12. The program of the congress is planned in four sections: the biological sciences; clinical medicine; psychology and the social sciences; and social welfare. Each section will hold scientific sessions for the presentation of papers, and four scientific sessions will meet simultaneously. There will be two plenary sessions and at least one open, public meeting. English will be the official language for the congress. The registration fee will be $25 for all who register before May 31; thereafter the registration fee will be $30. Those desiring to register in advance should so inform the president of the congress, Mr. Louis Kuplan, P. O. Box 2103, Sacramento 10, Calif.

Award for Paper on Biological Psychiatry.—The Society of Biological Psychiatry is offering an annual award made possible by the A. E. Bennett Neuropsychiatric Research Foundation. The A. E. Bennett Award of $500, part of which is to be used for traveling expenses to the society's meeting, will preferably be given to a young investigator not necessarily a member of the Society of Biological Psychiatry, for work which has recently been accomplished and not published. The paper will be read as part of the program of the annual meeting and will be published with the other papers read at that meeting in the book, "Biological Psychiatry," volume III. The honorarium will be awarded at the annual banquet. Submit papers in quadruplicate to Dr. Harold E. Himwich, Chairman, Committee of Award, Galesburg State Research Hospital, Galesburg, Ill. Deadline for manuscripts is April 30.

Meeting of Methodist Hospitals Group.—The annual convention of the National Association of Methodist Hospitals and Homes will be held Feb. 16-18 at the Deshler-Hilton Hotel, Columbus, Ohio, with Mr. Victor B. Hann, president of the association, Mechanicsburg, Pa., presiding at the opening general assembly. Secretary of Health, Education, and Welfare Arthur S. Flemming will give the keynote address at the first general assembly, Feb. 17. Group meetings will be held Feb. 17-18 and among the themes to be considered are the following: employee-employer relations, sharing today's administrative problems, and standards for nursing care. A discussion on preparation and recommendations for the White House Conference on Aging is planned and a panel discussion on Feb. 17 will consider "Our Common Objectives and How We Attain Them." A banquet will be held the evening of Feb. 17. For information, write the Board of Hospitals and Homes of the Methodist Church, 740 Rush St., Chicago 11.

Scholarships in Allergy for Students.—The Scientific and Educational Council of the Allergy Foundation of America announced the availability of a limited number of quarterly or summer scholarships at $600 each in approved medical schools in the United States and Canada. These scholarships are available to students who have "creditably completed" their second or third year in medical school and are to be for a minimum of eight weeks during which the student will receive training and experience both in clinical and research allergy. Each medical school has been invited to submit the name of one applicant through the dean's office with a letter from the dean in support of the candidate's application, outlining the candidate's medical school record, the proposed research project, and under whose sponsorship it will be carried out. Direct applications from students will not be considered. All applications must be filed no later than March 1 and should be sent to Dr. Robert A. Cooke, Chairman, Scientific & Educational Council, Allergy Foundation of America, 801 Second Ave., New York 17. This program of student summer scholarships was initiated by the foundation in 1956, when 10 such scholarships were awarded. Twenty scholarships were awarded in 1957, 22 in 1958, and 25 in 1959.

Council for Baby Care Formed.—Ernest G. Osborne, Ph.D., professor of education and associate in the Guidance Laboratory, Teachers College, Columbia University, New York City, is chairman of the board of the new organization known as the National Baby Care Council. The board of directors includes persons in medicine, public health, education, nursing, social service, hospitals, research, community organization, and communications. "The purpose of the National Baby Care Council is to concentrate attention on the baby from birth to the age of about two years," Dr. Osborne said. The council will attempt the following:

Bring into one body of knowledge all that is known about baby health, education, and welfare;
Identify areas in which more knowledge is needed and sponsor or recommend research to fill the gaps;
Serve as a channel of communication between those (professions) concerned with baby care;
Make information on baby care available, in understandable terms, to mother, family, professions, and community.

Financial support for the National Baby Care Council comes from the nation's diaper service industry. The council will conduct its program through an organization of professional committees. Each committee will be under the direction of a member of the board of directors selected from the professional field in which the committee functions. Two immediate projects to be sponsored by the council are the publication of a mother's handbook on the prevention of diaper rash and a training course for teenage girls in baby sitting. The address of the council is 1620 Locust St., Philadelphia 3.

Society News.—The **American Board for Certification in Orthotics and Prosthetics, Inc.,** held its annual meeting at Dallas, Texas, Oct. 20. Dr. Roy M. Hoover, Roanoke, Va., was the retiring president of the board. The new officers are: president, Howard Thranhardt, C. P., Atlanta, Ga.; vice-president, Dr. Eugene E. Record, Boston; secretary-treasurer, M. P. Cestaro, Washington, D. C. Dr. George T. Aitken, of Grand Rapids, Mich., was elected to the board by nomination of the American Academy of Orthopaedic Surgeons. Alvin Muilenburg, C. P., of Houston, Texas, was elected to the board by nomination of the American Orthotics and Prosthetics Association. Mr. Glenn E. Jackson is executive director of the board, with headquarters at 919 18th St., N.W., Washington, D. C.——**Phi Lambda Kappa,** medical professional fraternity, announced the election of the 1960 executive officers. Dr. Edward L. Axelman, Darby, Pa., is the new fraternity president; president-elect is Dr. Benjamin F. Bornstein, Boston. Reelected secretary is Dr. Abram H. Persky, 1205 Spruce St., Philadelphia, and reelected treasurer is Dr. Lawrence J. Thomas, Washington, D. C.——Herold R. Cox, Sc.D., was elected president of the **Society of American Bacteriologists.** Dr. Cox, director of virus research at Lederle Laboratories Division, American Cyanamid Company, is the first representative of industry ever elected to the post. His term will begin July, 1960. The new vice-president is Dr. John E. Blair, New York City. E. M. Foster, Ph.D., Madison, Wis., and John H. Bailey, Ph.D., of the Sterling-Winthrop Research Institute, will continue as secretary and treasurer, respectively.

Meeting on Pediatrics in Atlantic City.—The spring session of the American Academy of Pediatrics will be held April 20-22 at the Chalfonte-Haddon Hall, Atlantic City, under the presidency of Dr. William W. Belford, San Diego, Calif. Seven panel sessions are planned with the following titles and moderators:

What Kills Newborn Infants, Dr. Stuart S. Stevenson, Jersey City.
The Time to Operate on a Patient with Congenital Heart Disease, Dr. Daniel F. Downing, Philadelphia.
Present Status of Poliomyelitis Immunization, Dr. Joseph Stokes Jr., Philadelphia.
Drug Therapy in Pediatrics, Dr. Hans G. Keitel, Philadelphia.
Eastern Equine Encephalomyelitis, Dr. Roscoe P. Kandle, Trenton, N. J.
Neoplasms in Infants and Children, Dr. James B. Arey, Philadelphia.
Can the New Pediatrics be Practiced, Dr. Carl C. Fischer, Philadelphia.

A symposium, "What the 1960 White House Conference on Children and Youth Means to Pediatrics," is planned for the morning of April 22. Television presentations to be shown concurrently with the general sessions daily will include pediatric dermatology, pediatric orthopedics, pediatric radiology, practical ophthalmology for pediatricians, pediatric asthma, and pediatric endocrinology. Technical and scientific exhibits are planned. A program of entertainment will include the banquet at 8 p. m., April 21. Registration fee for members is $6 and for nonmembers out of school more than five years, $25. For information, write the executive office of the academy, 1801 Hinman Ave., Evanston, Ill.

Research Fellowship Program.—The Southeast Asia Treaty Organization through the Conference Board of the Associated Research Council Committee on International Exchange of Persons, announced its research fellowship program for 1960-1961. The aim of the SEATO Program is to encourage the study and research (preferably leading to publication) of such social, economic, political, cultural, scientific, and educational problems as "give insight into the present needs and future development of Southeast Asia and the Southwest Pacific, viewed against a background of SEATO objectives." A limited number of advanced research fellowships is offered for 1960-1961 to candidates from member states (Australia, France, New Zealand, Pakistan, the Philippines, Thailand, the United Kingdom, and the United States). A candidate must be a national of a member state and should plan to undertake his research in SEATO countries situated within the treaty area (the general area of Southeast Asia, including also the entire territories of the Asian Parties, and the general area of the Southwest Pacific, not including the Pacific area north of 21°30′ north latitude). Study in other countries may be authorized only under exceptional circumstances. The applicant's project should be of interest to SEATO and, preferably, to two or more SEATO member countries, rather than to a single one, but should not involve an extravagant travel plan. Grants are intended for well-established scholars. Candidates will be selected on the basis of their special aptitude and experience for carrying through a major project of research. Academic qualifications (the doctoral degree or its equivalent), professional experience beyond the completion of training, and published material will be taken into account. Preliminary screening of American candidates will be by the Committee on International Exchange of Persons of the Conference Board of Associated Research Councils, which will recommend candidates to the Department of State and the President's Board of Foreign Scholarships. It is expected that only one or two grants will be available to candidates from the U. S. The grant will provide a monthly allowance of $400 and tourist-class return air travel to the country or countries of research. Grants may be authorized for periods of from 4 to 10 months. Application forms and information may be obtained from the Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Ave., Washington 25, D. C. Applications should be submitted no later than March 1.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

American Board of Anesthesiology: *Written.* Various locations, June 24. Final date for filing application was January 10. *Oral.* Miami Beach, April 25-30. Applications already on file. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

American Board of Internal Medicine: *Oral.* San Francisco, March 30-April 1; New York City, Nov. 14-17. Closing date for filing application is Jan. 2 and July 1. *Written.* Oct. 17. Closing date for filing application is May 1. *Oral. Gastroenterology.* Philadelphia, March 11-12. Final date for filing application was January 15. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

American Board of Neurological Surgery: Examination given twice annually, in the spring and fall. St. Louis, April 10-12. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

American Board of Obstetrics and Gynecology: *Part II, Oral and Clinical.* Chicago, April 11-16. Final date for filing application was August 1. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

American Board of Ophthalmology: *Written.* Jan. 23, 1961. Deadline for filing applications is July 1. *Oral.* San Francisco, May 9-13; Chicago, Oct. 3-7. Sec., Dr. Merrill J. King, Box 236 Cape Cottage Branch, Portland, Maine.

American Board of Orthopaedic Surgery: *Part I,* Nashville, Denver and Philadelphia, Apr. 13-14. Deadline for receipt of applications was Nov. 30. *Oral and Written, Part II.* Miami Beach, Jan. 3-5, 1961. Final date for filing application is July 1. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

American Board of Otolaryngology: *Oral,* Chicago, Oct. 3-6. Final date for filing application is April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

American Board of Pathology: Memphis, April 21-23. Final date for filing application is March 7. *Examination in Forensic Pathology.* Memphis, April 22. Final date for filing application is March 7. Sec., Dr. Edward B. Smith, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

American Board of Pediatrics: *Written.* New York City, January 1961. Final date for filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

American Board of Physical Medicine and Rehabilitation: *Oral and Written.* New York, June 17-18. Sec., Dr. Earl C. Elkins, Mayo Clinic, Rochester, Minn.

American Board of Plastic Surgery: *Oral and Written.* Milwaukee, May 1960. Final date for filing application was January 1. Corresponding Secretary, Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

American Board of Proctology: *Oral and Written, Parts I and III,* Philadelphia, Sept. 24. Final date for filing application is June 30. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

American Board of Psychiatry and Neurology: San Francisco, March 14-15; New York, New York, Dec. 12-13. *Child Psychiatry.* Chicago, April 25-26. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

American Board of Radiology: *Examination.* Cincinnati, June 6-10; Dec. 5-9. Deadline for filing applications for the June examination was Jan. 1. Filing deadline for the December examination is July 1. A special examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

American Board of Surgery: *Oral Examinations (Part II):* New Orleans, Mar. 14-15; Kansas City, Kans., May 16-17; and Los Angeles, May 19-20. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

Board of Thoracic Surgery: *Oral.* May 1960. Final date for filing application was Dec. 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

American Board of Urology: *Written.* December. *Oral-Clinical.* Chicago, February 1961. Exec. Sec., Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 26.

GOVERNMENT SERVICES

PUBLIC HEALTH SERVICE

Mental Health Conference.—The conference of the surgeon general of the Public Health Service with state and territorial mental health authorities in January recommended that:

1. The Secretary of Health, Education, and Welfare propose to the Congress legislation to amend existing social security laws so that they do not discriminate against persons with any type of illness, mental or physical, and in the mean time that the present wording of the portion of the Social Security Act governing public assistance benefits be interpreted so as to specify that only persons physically residing in a mental hospital be excluded from assistance benefits.
2. General hospitals, particularly teaching hospitals, be encouraged to admit alcoholics for treatment.
3. The Public Health Service be requested to provide short courses in appropriate places throughout the country to give instruction and orientation in the development of alcoholism program activities.
4. Wherever appropriate, alcoholism services be incorporated with other community activity and that mental health centers, if they are not now serving alcoholics, be encouraged to do so.
5. The Public Health Service provide leadership in working with the states in research on the emotional problems of children.
6. The Public Health Service conduct or support a survey of current patterns of mental health education and information programs of the various states with particular attention to program content, staff, techniques, evaluation methods, and results and publish a report that can be used as a resource manual to be made available especially to state mental health authorities.
7. The Public Health Service encourage the development of comprehensive diagnostic and treatment services for mentally retarded persons, integrated with other medical and related services at the local community level.
8. The Public Health Service investigate through sociological and epidemiologic studies the needs of mentally retarded and border-line adults and the resources available for them.
9. The Department of Health, Education, and Welfare emphasize in its training and assistance programs the subject of mental retardation.
10. Mental retardation be included as a major agendum at the 1961 conference of the surgeon general with state and territorial mental health authorities.
11. State mental health authorities be supplied with copies of the report, "School Mental Health Activities of State Mental Health Authorities," and that each state mental health authority be requested to provide supplementary information about its activities in the school mental health area to be included in a periodic revision of the report.
12. Wherever feasible, the state mental health authorities take the initiative in establishing appropriate liaison mechanisms with departments of education so that they can together, in a mutual relationship and on a joint basis, analyze and develop the comprehensive school mental health programs in the state.
13. The staff for school mental health consultation services of the community services branch be expanded in order to provide more intensive services to the states in which a need for additional services exists.
14. The Public Health Service expand the programs for the training of school mental health personnel.
15. The Public Health Service be encouraged to contract for special studies in school mental health programs.

Hospital to Close.—The Public Health Service Hospital for tuberculosis patients at Manhattan Beach, Brooklyn, will be closed on June 15. Beneficiaries of the service suffering from tuberculosis will receive care at selected Public Health Service hospitals or at a nonservice hospital under a contractual arrangement. Employees will be given all possible assistance in finding employment with other Public Health Service installations and other federal and private agencies. The decision to close the 350-bed hospital, operated by the Public Health Service since 1950, was made because of the decreasing number of patients with tuberculosis. Since 1955 the average number of patients has declined from 339 to 210. Meanwhile, the annual cost of operation rose from $1,334,000 to $1,610,000.

New Appointments.—Dr. Howard P. Rome, professor of psychiatry at the graduate school of medicine, University of Minnesota, Mayo Foundation for Medical Education and Research, Rochester, Minn.; Dr. John T. Cowles, professor of psychology at the school of medicine, University of Pittsburgh; and Dr. Robert B. Howard, dean of the University of Minnesota Medical School, Minneapolis; were each appointed to serve a three-year term on the selection committee for the senior research fellowship program of the National Institutes of Health.

New Publication.—The importance of area-wide planning in the development of a coordinated hospital system is stressed in the Public Health Service publication, "Principles for Planning the Future Hospital System," which is a report of the proceedings of regional conferences held in Chicago, New Orleans, Salt Lake City, and Washington, D. C., in April and May, 1959, under the joint sponsorship of the American Hospital Association and the Public Health Service.

Training in Public Health.—The Public Health Service is accepting applications from professional health workers for graduate training in public health for the 1960-1961 academic year. Congress first established this program in 1956. Over the past four years 158 physicians have been awarded such traineeships. The awards provide stipends for living expenses of the trainees in addition to tuition and fees. Applications should be submitted by March 1.

Venereal Disease on Increase.—The incidence of early infectious syphilis for the fiscal year 1959 was up 22.8% over that of fiscal 1958. If the current trend continues, the number of persons with early infectious syphilis will soar to over 10,000 in the fiscal year 1960. This rise was accompanied by a 7.8% rise in the incidence of gonorrhea for the same period.

Retirement.—Dr. C. J. Van Slyke, deputy director of the National Institutes of Health, retired after 30 years' service. He was appointed the first deputy director of the Institutes in 1958 after having served as associate director since 1952. Dr. Kenneth M. Endicott, presently associate director for training programs, will be given additional responsibilities involving the grants program.

FOOD AND DRUG ADMINISTRATION

Court Actions.—Bulk wheat, flour, and corn grits contaminated by rodents and insects accounted for 214 of the 500 tons of unfit foods removed from the market in November. Spoilage, parasitic cysts, and filth were found in 44 tons of haddock fillets, breaded shrimp, whitefish, trout, and anchovies. Nearly 30 tons of canned tomatoes and catsup containing fly eggs and maggots were seized in 10 actions. Another 30 tons consisted of moldy frozen blueberries, spoiled apricot concentrate, and insect-contaminated maraschino cherries. Spoilage in a 15-ton shipment of frozen chickens caused its removal from the market. Seized as economic cheats were 92,000 tablets of low-strength vitamin products and 19 tons of other foods including canned peas and fruit jams failing to meet requirements of the respective definitions and standards of identity, and canned peppers and raw popcorn with less of the product than was declared on the label.

Eleven of the 19 drugs and devices seized were alleged to be misbranded by false and misleading claims. Three nonprescription products containing a so-called "appetite depressant" were offered to reduce weight. A plastic "breather bag" was offered for $1 as a treatment for foot and leg cramps. Users of the bag were instructed to do the following actions five times: take a deep breath, exhale into the bag through the mouth, and inhale contents of the bag through the nose. A vitamin product in timed-release capsules was offered with claims that it would provide "pep in minutes that lasts for hours." The stimulant in each capsule was found to be caffeine in an amount equal to that provided in 1 to 1.5 cups of coffee. A "prescription dentrifice" sold directly to the public was represented in leaflets as a treatment for bleeding gums, pyorrhea, gingivitis, and other oral conditions.

New Drug Removed from the Market.—A California manufacturer's authorization to market a new drug was revoked and the product taken off the market because the company completely disregarded the specific conditions of production and use that it proposed in obtaining authorization to market the product (Pre-Creatine). This drug was offered for increasing available energy to muscles and nerves damaged by cardiac and neuromuscular diseases. The revocation was based on the fact that (1) manufacturing, packaging, and labeling of the product was performed by a different firm than was named in the application for authorization, (2) other ingredients than those listed were used, (3) the approved control procedures for identification and assay of raw materials and the finished product were not followed, and, (4) an important ingredient was obtained from a different source than was stated. Such complete disregard by the manufacturer of the essential safety precautions included in a new drug application is rare.

Purveyor of Rotten Eggs Jailed.—Harry Cohen, convicted principal in the East Coast diversion of rotten incubator reject eggs into foods, pleaded guilty to charges of violating terms of a five-year probation and was sentenced to three months in jail. Inspectors proved that Cohen was back in business between Jan. 16 and March 5 and was responsible for buying incubator reject eggs from Connecticut hatcheries and shipping them to New York. There these rotten eggs would have been broken and packed for sale in 30-pound cans as frozen whole eggs. The court ordered that Cohen's probation be continued when his jail sentence expires.

Voluntary Corrective Actions.—Two Washington state bakers took the lead in voluntary plant improvements with programs costing $64,400. A total of $174,965 went into 19 individual plant improvements to assure production of clean, wholesome products, according to food manufacturers and warehousemen. An additional 82 actions by food firms to protect the public resulted in the destruction or diversion to nonfood use of 246 tons of unfit foods. Drug firms voluntarily destroyed old and substandard drugs valued at $2,968.

DEATHS

Baert, George Henry Ⓜ Grand Rapids, Mich.; University of Pennsylvania Department of Medicine, Philadelphia, 1893; served on the board of education; died Nov. 5, aged 89.

Ballard, Marshall Paul Ⓜ Delphos, Kan.; University of Kansas School of Medicine, Kansas City, Kan., 1936; interned at St. Mary's Hospital in Kansas City, Mo.; served as health officer of Ottawa County; on the staff of the St. Joseph's Hospital in Concordia; died Nov. 20, aged 50.

Barnett, William Edwin Ⓜ Dallas, Texas; Indiana University School of Medicine, Indianapolis, 1931; interned at the Indiana University Hospitals, Indianapolis, where he served a residency; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; served on the faculty of the University of Texas Southwestern Medical School; veteran of World War II and held the American Defense and Pacific Theatre medals; associated with the Baylor University Hospital and the Parkland Memorial Hospital; on the staff of St. Paul's Hospital, where he died Nov. 2, aged 54.

Bartholomew, Don Clio Ⓜ San Diego, Calif.; Detroit College of Medicine and Surgery, 1916; retired from the U. S. Army June 30, 1935; died in the U. S. Naval Hospital Oct. 4, aged 71.

Baumgartner, Conrad, St. Louis; Barnes Medical College, St. Louis, 1895; died in the Alexian Brothers Hospital Nov. 19, aged 85.

Beckford, Samuel McDonald, Henderson, N. C.; Boston University School of Medicine, 1917; died in the Jubilee Hospital Sept. 4, aged 74.

Beecher, Clarence H. Ⓜ Burlington, Vt.; born in Granville, N. Y., Oct. 9, 1877; University of Vermont College of Medicine, Burlington, 1900; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians, of which he was at one time governor; for many years on the faculty of his alma mater, where he served as dean from 1941 to 1945; past-president and secretary of the Vermont State Medical Society, of which he was an honorary member and recipient of the society's distinguished service award; past-president of the Vermont Heart Association; served as mayor of Burlington; consulting physician at the Fanny Allen Hospital in Winooski, Bishop De Goesbriand Hospital, and the Mary Fletcher Hospital; in 1958 the honorary degree of doctor of science was conferred upon him by his alma mater; died in the Mary Fletcher Hospital Nov. 21, aged 82.

Berczeller, Arpod Ⓜ Staten Island, N. Y.; Medizinische Fakultät der Universität, Vienna, Austria, 1929; interned at the Sea View Hospital, where he was associated with the department of bacteriology; died in the Madison Avenue Hospital, New York City, Nov. 28, aged 55.

Bergstein, Joseph Ⓜ Brooklyn; University and Bellevue Hospital Medical College, New York City, 1929; member of the American Academy of General Practice; died Oct. 10, aged 55.

Birchard, Fred Sherman Ⓜ Montrose, Pa.; Medico-Chirurgical College of Philadelphia, 1903; past-president of the Susquehanna County Medical Society; affiliated with the Robert Packer Hospital in Sayre; died Nov. 12, aged 79.

Boccelato, Salvador L. Ⓜ San Antonio, Texas; Memphis (Tenn.) Hospital Medical College, 1913; veteran of World War I; on the staff of Santa Rosa Hospital, where he died Nov. 6, aged 70.

Bohn, Julius Charles Ⓜ Tacoma, Wash.; Washington University School of Medicine, St. Louis, 1901; veteran of World War I; once named "outstanding general practitioner of the year" by the Pierce County Medical Society; died in the Tacoma General Hospital Oct. 31, aged 83.

Bray, Emmett Perleyman, Richmond, Va.; Medical College of Virginia, Richmond, 1922; died Nov. 7, aged 71.

Brecker, Francis Wellington Ⓜ Hartford, Conn.; Tufts College Medical School, Boston, 1928; member of the American Academy of Dermatology and Syphilology; at one time health officer for the town of East Hartford; on the staffs of the Institute of Living, J. J. McCook Memorial Hospital, and St. Francis Hospital, where he died Nov. 3, aged 58.

Brewster, Guy Otis, Florida City, Fla.; Jefferson Medical College of Philadelphia, 1896; died Oct. 28, aged 90.

Britt, Patrick Francis, Syracuse, N. Y.; Syracuse University College of Medicine, 1922; veteran of World War I; for many years associated with St. Mary's Hospital; courtesy member of the staff of St. Joseph's Hospital; died Nov. 14, aged 66.

Ⓜ Indicates Member of the American Medical Association.

Browe, Evelyn Lilian, Brainerd, Minn.; University of Minnesota Medical School, Minneapolis, 1928; member of the American Society of Anesthesiologists; died in St. Joseph's Hospital Aug. 25, aged 57.

Brown, William Marion Ⓜ Livingston, Tenn.; Lincoln Memorial University Medical Department, Knoxville, 1918; died Nov. 5, aged 79.

Cary, Edward Austin Ⓜ Ann Arbor, Mich.; Tulane University School of Medicine, New Orleans, 1947; interned at the University Hospital, where he served a residency; specialist certified by the American Board of Psychiatry and Neurology; on the faculty of the University of Michigan Medical School; veteran of World War II; an officer in the U. S. Naval Reserve from 1950 to 1952; on the staff of the Veterans Administration Hospital; died Nov. 24, aged 35.

Clay, Frank Homer, Longwood, Fla.; Minneapolis College of Physicians and Surgeons, 1910; died Nov. 6, aged 75.

Conwell, John Berchman, Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1935; served on the staffs of the Wills Eye Hospital and the Hahnemann Hospital; died Nov. 28, aged 51.

Costolow, William Evert Ⓜ Los Angeles; born in Kirksville, Mo., June 13, 1892; University of Pennsylvania School of Medicine, Philadelphia, 1916; on the faculty of the University of Southern California School of Medicine; specialist certified by the American Board of Radiology; member of the Radiological Society of North America, Inc., of which he was past-vice-president, American College of Radiology, and the American Radium Society, of which he was past-president and secretary; fellow of the American College of Physicians; past-president of the Los Angeles County Medical Association and past-vice-president of the Los Angeles Branch of the American Cancer Society; consultant, Los Angeles Tumor Institute; served as president of the Albert Soiland Cancer Foundation; past-chairman, tumor board, Los Angeles County General Hospital; associated with the California, St. Vincent's, and Santa Fe Coast Lines hospitals; at one time a fellow at the Mayo Clinic in Rochester, Minn.; veteran of World Wars I and II; died in the Good Samaritan Hospital Nov. 22, aged 66.

Couey, Elmer J. Ⓜ Santa Ana, Calif.; College of Physicians and Surgeons of San Francisco, 1900; past-president of the Fresno County Medical Society; for many years practiced in Fresno, where he was associated with the Fresno County Health Department; served as assistant county health officer in Fresno County; died Oct. 25, aged 82.

Cubbins, William Robert Ⓜ Dundee, Ill.; Northwestern University Medical School, Chicago, 1900; member of the founders group of the American Board of Surgery; member of the Western Surgical Association; fellow and a founder of the American College of Surgeons; served on the faculty of Loyola University School of Medicine in Chicago, where he was on the staffs of St. Luke's and Cook County hospitals; died in the Sherman Hospital, Elgin, Nov. 15, aged 85.

Culbreath, Louis W., Stanton, Tenn.; Memphis (Tenn.) Hospital Medical College, 1899; died in Jackson Oct. 4, aged 90.

Curran, Harold Joseph Ⓜ Waterbury, Conn.; Tufts College Medical School, Boston, 1924; fellow of the American College of Surgeons; member of the Industrial Medical Association; died in the Waterbury Hospital Nov. 4, aged 59.

Donahue, John Leo Ⓜ Tucson, Ariz.; Jefferson Medical College of Philadelphia, 1910; specialist certified by the American Board of Psychiatry and Neurology; veteran of World War I; served on the staffs of the Veterans Administration hospitals in Fort Bayard, N. M., and in Tucson; died Nov. 17, aged 73.

Ellis, Henry Avner Ⓜ Kiowa, Okla.; College of Physicians and Surgeons, Dallas, Texas, 1905; died in McAlester Nov. 13, aged 83.

Fasoldt, Laurence Otto Ⓜ Glendale, Ohio; University of Vermont College of Medicine, Burlington, 1937; interned at the St. John's Riverside Hospital in Yonkers, N. Y.; veteran of World War II; member of the Aero Medical Association; associated with the Fort Hamilton and Mercy hospitals in Fort Hamilton and the Maple Knoll Hospital, where he was secretary of the medical staff; died Nov. 22, aged 52.

Fullerton, Lynne Araunah Ⓜ Tacoma, Wash.; University of Minnesota Medical School, Minneapolis, 1916; specialist certified by the American Board of Preventive Medicine; in 1935 appointed medical inspector in the Indian Medical Service with headquarters in Spokane; for many years associated with the U. S. Public Health Service, retiring Sept. 1, 1950; veteran of World Wars I and II; died in the Madigan Army Hospital Sept. 11, aged 68.

Gibbons, Joel Marion Ⓜ Van Nuys, Calif.; born in Sweetwater, Texas, Aug. 12, 1911; College of Medical Evangelists, Loma Linda and Los Angeles, 1936; interned at the Los Angeles County Hospital in Los Angeles; on the faculty of his alma mater; certified by the National Board of Medical Examiners; specialist certified by the American Board of O[illegible] [illegible]mber of the American Academy [illegible] and Otolaryngology and the Aero Medical Association; fellow of the

International College of Surgeons; veteran of World War II; associated with St. Joseph's Hospital in Burbank, White Memorial Hospital in Los Angeles, and the Valley Hospital; died Nov. 16, aged 48.

Hallenbeck, Clive Ewer, Dunkirk, N. Y.; University of Michigan Medical School, Ann Arbor, 1907; on the staff of the Brooks Memorial Hospital; died Nov. 15, aged 77.

Harvey, John Ⓜ Lexington, Ky.; University of Pennsylvania School of Medicine, Philadelphia, 1920; certified by the National Board of Medical Examiners; specialist certified by the American Board of Internal Medicine; member of the American Rheumatism Association and the Central Society for Clinical Research; fellow of the American College of Physicians; veteran of World War II; chairman of the Lexington-Fayette County Board of Health; on the staffs of the Good Samaritan Hospital and St. Joseph's Hospital, where he died Nov. 14, aged 66.

Heath, George Dawson Jr. Ⓜ Madison, Va.; University of Louisville (Ky.) Medical Department, 1907; veteran of World War I; formerly health director of Bloomington, Ill.; died in Staunton Nov. 12, aged 75.

Henderson, James Alfred Ⓜ New Orleans; Medical Department of Tulane University of Louisiana, New Orleans, 1903; veteran of World War I; served as secretary-treasurer and chief sanitation officer of the New Orleans Board of Health; formerly secretary of the state board of medical examiners; for many years on the staff of the Charity Hospital; died in the Mercy Hospital Nov. 21, aged 78.

Hoover, Lawrence Hites, Clarksville, Va.; Medical College of Virginia, Richmond, 1920; died in South Boston Nov. 20, aged 65.

Hudson, Victor Talmadge Ⓜ Mobile, Ala.; University of Tennessee College of Medicine, Memphis, 1937; interned at the Kansas City General Hospital in Kansas City, Mo.; served a residency at St. Luke's Hospital in Bethlehem, Pa.; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; veteran of World War II; associated with the Mobile Infirmary, Providence Hospital, and the Mobile General Hospital; died Nov. 12, aged 47.

Hussey, Carlyle Perry Ⓜ Suffern, N. Y.; University of Pennsylvania Department of Medicine, Philadelphia, 1904; associated with the Tuxedo Memorial Hospital in Tuxedo Park and the Good Samaritan Hospital; consulting diagnostician with the Columbia-Presbyterian Medical Center in New York City; died Nov. 1, aged 80.

Jordan, Kenneth Laird Ⓜ Montclair, N. J.; born in Yonkers, N. Y., Dec. 1, 1920; New York University College of Medicine, New York City, 1945; interned at St. Claire's Hospital in New York City; served a residency at the Hospital for Crippled Children in Newark, Duke Hospital in Durham, N. C., and the North Carolina Orthopedic Hospital in Gastonia, N. C.; specialist certified by the American Board of Orthopaedic Surgery; certified by the National Board of Medical Examiners; member of the American Academy of Orthopedic Surgeons; fellow of the American College of Surgeons; from 1946 to 1948 served in the Medical Corps, U. S. Naval Reserve; on the staffs of the Hospital for Crippled Children in Newark, Hasbrouck Heights (N. J.) Hospital, Mountainside Hospital, Community Hospital, and the St. Vincent's Hospital, where he died Nov. 11, aged 38.

Judge, Francis Patrick Ⓜ Wilkes-Barre, Pa.; Jefferson Medical College of Philadelphia, 1924; specialist certified by the American Board of Urology; member of the American Urological Association; interned at the Philadelphia General Hospital and the Philadelphia Hospital for Contagious Diseases; veteran of World War II; associated with the Nesbitt Memorial Hospital, Kingston, and the Mercy Hospital; died Nov. 14, aged 58.

Kaplan, Herbert Ⓜ Collegeville, Pa.; Jefferson Medical College of Philadelphia, 1931; died in the Montgomery Hospital, Norristown, Nov. 24, aged 54.

Kauth, Phillip Merkel Ⓜ West Bend, Wis.; Wisconsin College of Physicians and Surgeons, Milwaukee, 1909; on the staff of St. Joseph's Hospital, where he died Nov. 16, aged 76.

Kirk, Robert Dixon Ⓜ Tupelo, Miss.; University and Bellevue Hospital Medical College, New York City, 1922; member of the Southeastern Surgical Congress; fellow of the International College of Surgeons and the American College of Surgeons; veteran of World War II; on the staff of the North Mississippi Community Hospital; died in Dallas, Texas, Nov. 16, aged 61.

Klemann, George Francis, New York City; Long Island College Hospital, Brooklyn, 1903; staff physician with the New York Regional Blood Program of the American Red Cross; died in the Manhattan General Hospital Nov. 12, aged 78.

Kline, Walter Lee Jr., Messick, Va.; George Washington University School of Medicine, Washington, D. C., 1935; veteran of World War II; formerly associated with the Veterans Administration; died in the Veterans Administration Center, Kecoughton, Nov. 6, aged 54.

Knapp, John Rudolph Ⓜ New York City; University of Pennsylvania Department of Medicine, Philadelphia, 1894; member of the American Psychiatric Association; for many years associated with the Manhattan State Hospital; died near Lansdale, Pa., Nov. 4, aged 89.

Konigmacher, Adam Hiestand Ⓜ Fresno, Calif.; Creighton University School of Medicine, Omaha, 1913; past-secretary of the Fresno County Medical Society; veteran of World War I; for many years served on the city board of health; died Nov. 20, aged 69.

Krupp, Christian George, Grand Rapids, Mich.; Loyola University School of Medicine, Chicago, 1927; died Nov. 2, aged 59.

Lanphier, Vernard Anthony, San Gabriel, Calif.; Creighton University School of Medicine, Omaha, 1908; veteran of World War I; served on the staff of Creighton Memorial St. Joseph's Hospital, Omaha; died Nov. 3, aged 76.

Lavanture, Mary Leona Jacob, Portland, Ore.; University of Oregon Medical School, Portland, 1913; died Oct. 6, aged 69.

Lerch, Donald G. Ⓜ Milton, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1903; for many years on the staffs of the Suburban General Hospital in Bellevue and the Shadyside Hospital in Pittsburgh; died in the George F. Geisinger Memorial Hospital in Danville Nov. 19, aged 80.

Lincoln, Mary Cain Ⓜ Sister Bay, Wis.; Rush Medical College, Chicago, 1905; died in Algoma (Wis.) Memorial Hospital Oct. 31, aged 85.

Lynn, Leo Joseph, Medford, Mass.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1925; chief physician at the Belchertown State School for Boys; served on the staffs of the Chelsea (Mass.) Memorial Hospital and the Whidden Memorial Hospital in Everett; died Nov. 6, aged 61.

Mackie, Janet Welch Ⓜ Washington, D. C.; L.R.C.P., London and M.R.C.S., of England, 1926; formerly taught at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.; in 1952 became a consultant for the Point Four Program of the International Cooperation Administration; formerly attached to the World Health Organization in Geneva, Switzerland; served with the U. S. Public Health Service Reserve; the British government awarded her the Order of the British Empire for her work in Africa; died Nov. 24, aged 65.

McCall, John Gordon Ⓜ Brady, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1901; veteran of World War I; for 50 years county health officer; vice-president and director of the Commercial National Bank; founded the Brady Hospital, where he died Nov. 20, aged 83.

McDaniel, John Riley Sr. Ⓜ Patterson, Mo.; University of the South Medical Department, Sewanee, Tenn., 1899; died in the Doctors Hospital, Poplar Bluff, Oct. 26, aged 86.

McGarvey, Henry Earl Ⓜ Bronxville, N. Y.; Vanderbilt University College of Medicine, Nashville, Tenn., 1914; veteran of World War I; chief surgeon of the Westchester County Parkway Police; past-president of the Westchester County Medical Society; associated with the Lawrence Hospital, where he died Nov. 7, aged 71.

McGogney, Clyde Bernard Ⓜ Midland, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1905; died in New Brighton Nov. 10, aged 80.

McKinnon, John D. Ⓜ Highland Park, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1908; served on the staff of the Highland Park General Hospital, where he died Nov. 6, aged 80.

McNamee, Owen James, St. Louis; St. Louis University School of Medicine, 1921; veteran of World War I; died in the Firmin Deslodge Hospital Oct. 30, aged 62.

McNeill, James Hubert Ⓜ North Wilkesboro, N. C.; George Washington School of Medicine, Washington, D. C., 1926; fellow of the American College of Physicians; member of the American Trudeau Society; past-president of the Wilkes-Alleghany Counties Medical Society; on the staff of the Wilkes-General Hospital, where he died Nov. 19, aged 58.

Maher, Aldea Ⓜ New Orleans; Tulane University School of Medicine, New Orleans, 1919; specialist certified by the American Board of Pathology; fellow of the College of American Pathologists; member of the American Society of Clinical Pathologists; professor of medical technology and special lecturer of physiology and chemistry at Loyola University; formerly on the faculty of her alma mater; served on the staff of the Hotel Dieu; died in the Baptist Hospital Nov. 20, aged 67.

Marsden, George Albert Ⓜ Oswego, N. Y.; Syracuse University College of Medicine, 1920; fellow of the American College of Surgeons; served as city health officer of Oswego; on the staff of the Oswego Hospital; died Nov. 15, aged 64.

Marshall, Clifford Cleland Ⓜ Sharon, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1900; veteran of World War I; associated with the Sharon General Hospital, where he served as chief of staff and where he died Nov. 8, aged 85.

Martin, William Claude, Put-in-Bay, Ohio; Western Reserve University Medical Department, Cleveland, 1908; formerly practiced in Monroeville, where he served as mayor; died Sept. 13, aged 76.

Mercer, Arthur Henry Ⓜ Las Vegas, Nev.; Dalhousie University Faculty of Medicine, Halifax, N. S., Canada, 1944; specialist certified by the American Board of Pathology; certified by the National

Board of Medical Examiners; member of the College of American Pathologists and the American Society of Clinical Pathologists; died Nov. 20, aged 40.

Millea, William Lawrence Ⓜ Baltimore; Johns Hopkins University School of Medicine, Baltimore, 1912; veteran of World War I; served on the staff of the Church Home and Hospital, where he died Nov. 17, aged 73.

Miller, Minor W. Ⓜ Evansville, Ind.; Indiana University School of *Medicine, Indianapolis, 1912*; past-president of the Vanderburgh County Medical Society; a charter member and past-president of the Indiana State Health Officers Association; charter member of the American Association of Public Health Physicians; director of the city-county department of health; associated with the Welborn Memorial Baptist Hospital and the Protestant Deaconess Hospital, where he died Nov. 17, aged 72.

Modance, Abraham M. Ⓜ New York City; New York Homeopathic Medical College and Flower Hospital, New York City, 1922; member of the American Society of Anesthesiologists; died in the Westchester Square Hospital Nov. 24, aged 68.

Moore, Julian Alison Ⓜ Asheville, N. C.; born in Abbeville, Ga., Oct. 31, 1896; University of Pennsylvania School of Medicine, Philadelphia, 1918; specialist certified by the American Board of Thoracic Surgery; member of the founders group of the American Board of Surgery; certified by the National Board of Medical Examiners; past-president of the Buncombe County Medical Society and the 10th District Medical Society; served as vice-president of the Medical Society of the State of North Carolina; member of the Southern Surgical Association, Southeastern Surgical Congress, American Association for Thoracic Surgery, and the American Trudeau Society; fellow of the American College of Surgeons; served as director and secretary-treasurer of the Asheville Medical Library; consultant, Veterans Administration Hospital in Oteen; associated with St. Joseph's Hospital and the Memorial Mission Hospital of Western North Carolina; served on the staff of the Western North Carolina Sanatorium in Black Mountain, where in 1953 a wing was dedicated in his honor; died Nov. 7, aged 63.

Murphy, Jennie C., Yankton, S. D.; the Hahnemann Medical College and Hospital, Chicago, 1893; city street commissioner from 1919 to 1924; formerly county coroner; on the staff of the Sacred Heart Hospital, where she died Nov. 3, aged 94.

Neal, William Elmer Ⓜ Huntington, W. Va.; Medical College of Ohio, Cincinnati, 1906; formerly mayor, member of the board of park commissioners, and a member of the state legislature; on the staff of St. Mary's Hospital, where he died Nov. 12, aged 84.

Neblett, Clarence P., Waverly, Va.; Medical College of Virginia, Richmond, 1896; served on the Sussex County school board; formerly secretary of the Sussex County Medical Society; died Nov. 18, aged 89.

Neely, Shade Durrett Ⓜ Muskogee, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1920; past-president of the East Central Oklahoma Medical Society; veteran of World Wars I and II; in 1937 appointed health superintendent of Muskogee County; on the staffs of the Muskogee General and Oklahoma Baptist hospitals; died Nov. 19, aged 62.

Neistadt, Isidore Irving Ⓜ Valley Stream, N. Y.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1929; veterans of World War II; on the staffs of the South Nassau Communities Hospital in Oceanside and St. Joseph's Hospital in Far Rockaway; died in South Nassau Communities Hospital, Oceanside, Nov. 30, aged 54.

Neuhaus, Hugo Ⓜ Freeport, N. Y.; Albert-Ludwigs Universität Medizinische Fakultät, Freiburg, Baden, Germany, 1909; specialist certified by the American Board of Pediatrics; fellow of the American Academy of Pediatrics; served in the German Army during World War I; served on the staffs of South Nassau Communities Hospital in Rockville Centre and the Doctors Hospital, where he died Nov. 24, aged 74.

Nicholas, Pike Calton, Spur, Texas; Louisville (Ky.) Medical College, 1907; died in the Spur Memorial Hospital Nov. 9, aged 78.

Otradovec, Joseph Henry Marie Ⓜ Chicago; Rush Medical College, Chicago, 1901; died in the Presbyterian-St. Luke's hospital Nov. 6, aged 86.

Ott, Charles Henry Jr. Ⓜ Elmira, N. Y.; Jefferson Medical College of Philadelphia, 1920; veteran of World War I; for many years member of the board of education; member of the courtesy staff of St. Joseph's Hospital, where he died Oct. 22, aged 67.

Ovary, Stephen Francis, New York City; Long Island College Hospital, Brooklyn, 1908; died Oct. 13, aged 77.

Patterson, Job Caldwell Ⓜ Cuthbert, Ga.; born in 1892; Atlanta College of Physicians and Surgeons, 1913; member of the Southeastern Surgical Congress and the Industrial Medical Association; fellow of the International College of Surgeons and the American College of Surgeons; past-president of the Medical Association of Georgia; veteran of World War I; medical director of the Patterson Hospital; a trustee of the Andrew College; a member of the Randolph County Board of Health; county physician; a director of the Citizens Bank and of Randolph County Federal Savings & Loan Association; past-president of the Cuthbert Rotary Club; died Nov. 8, aged 67.

Parker, James Mitchell Ⓜ Portland, Maine, Harvard Medical School, Boston, 1934; served on the faculty of his alma mater; certified by the National Board of Medical Examiners; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; consultant, Webber Hospital, Biddeford; served on the staffs of the Maine Medical Center and Mercy Hospital; died in the Johns Hopkins Hospital in Baltimore Nov. 18, aged 51.

Pflueger, Edwin H. Ⓜ Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1905; died in the Hahnemann Hospital Nov. 1, aged 76.

Pharr, John Newton Ⓜ New Iberia, La.; Tulane University School of Medicine, New Orleans, 1914; died Nov. 7, aged 70.

Phillips, John William, Arcadia, Calif.; George Washington University School of Medicine, Washington, D. C., 1921; member of the American Society of Anesthesiologists, Inc.; died Oct. 28, aged 72.

Pizzi, Frederick Athanasius Ⓜ Forest Hills, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1927; fellow of the American College of Surgeons; served on the staff of the Brooklyn Hospital, where he died Nov. 21, aged 57.

Remy, Lorenzo Albert Ⓜ Chicopee Falls, Mass.; Boston University School of Medicine, 1927; medical examiner for the Fifth Hampden District; member of the staffs of the Holyoke and Providence hospitals in Holyoke; died in the Mercy Hospital, Springfield, Oct. 31, aged 59.

Richards, Clarence Alfred Ⓜ Rhinelander, Wis.; Rush Medical College, Chicago, 1902; member of the House of Delegates of the American Medical Association in 1909; served with the American Expeditionary Forces in France during World War I; formerly member of the state board of health; president of the First National Bank; once served as chief of staff of St. Mary's Hospital, where he died Nov. 14, aged 83.

Rizer, Robert Inskeep Ⓜ Wayzata, Minn.; Rush Medical College, Chicago, 1906; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the Endocrine Society; served on the faculty of the University of Minnesota Medical School in Minneapolis, where he was on the staff of the Northwestern Hospital; died Nov. 13, aged 76.

Rosenman, Jacob Daniel Ⓜ Akron, Ohio; Columbia University College of Physicians and Surgeons, New York City, 1916; died Oct. 21, aged 71.

Spiller, John Browder, Houston, Texas; University of Texas School of Medicine, Galveston, 1920; member of the Radiological Society of North America; veteran of World War I; died in the Medical Arts Hospital Oct. 31, aged 65.

Stubblebine, James Good Ⓜ Concord, Calif.; Rush Medical College, Chicago, 1936; served on the staff of the Camarillo (Calif.) State Hospital; civilian physician at the U. S. Naval Ammunition Depot; died Oct. 27, aged 63.

Thomas, Clifford Ward Ⓜ Mason City, Iowa; State University of Iowa College of Medicine, Iowa City, 1927; veteran of World War II; past-president of the Cerro Gordo County Medical Society; a member of the department of internal medicine of Park Clinic; on the staff of the Park Hospital; died Oct. 28, aged 57.

Thompson, George Farnsworth Ⓜ Chicago; Rush Medical College, Chicago, 1899; fellow of the American College of Surgeons; served on the faculty of his alma mater and the University of Illinois College of Medicine; past-president of the Chicago Surgical Society; associated with the Westlake Hospital in Melrose Park, Ill., Oak Park (Ill.) Hospital, and St. Anne's Hospital; for many years on the staff of Cook County Hospital; died Nov. 10, aged 84.

Thuringer, Joseph Marion Ⓜ Fayetteville, Ark.; Creighton University School of Medicine, Omaha, 1911; formerly on the faculty of Harvard Medical School in Boston, Tulane University School of Medicine in New Orleans, University of Oklahoma School of Medicine in Oklahoma City, and the University of Alabama School of Medicine in Mobile; retired from the Veterans Administration on July 2, 1956; died Oct. 28, aged 73.

Way, Julius, Cape May Court House, N. J.; Jefferson Medical College of Philadelphia, 1885; served as county clerk and county physician; author of "An Historical Tour of Cape May County"; died in the Burdette Tomlin Memorial Hospital Oct. 20, aged 99.

Wood, Frances Holmes, Tucson, Ariz.; New York Medical College and Hospital for Women, New York City, 1892; died Oct. 7, aged 94.

Zasly, Louis, Delray Beach, Fla.; Syracuse University College of Medicine, 1953; interned at the Queens General Hospital in Jamaica, N. Y.; served a residency at the Veterans Administration Hospital in Coral Gables; certified by the National Board of Medical Examiners; veteran of World War II; died Oct. 26, aged 33.

FOREIGN LETTERS

ECUADOR

Hepatopulmonary Amebiasis.—At a meeting of the Academia Ecuatoriana de Medicina in July, Drs. L. Arcos and J. Rodriguez of Quito reported a series of 21 patients who had amebic hepatitis with pulmonary complications. Symptoms had been present for 1 to 22 months prior to admission, with periods of exacerbation and partial remissions. Fever was present in 17 patients, but all had a dull thoracic pain radiating to the right shoulder. A productive cough with various amounts of blood in the sputum was observed in 18. Characteristically the sputum showed a uniform mixture of blood and mucus, resulting in an even pink rather than red color. This is not seen in other conditions. An enlarged and tender liver was present in 19 and dulness with fine rales at the base of the lungs was present in 15 of the patients. Roentgenograms revealed an elevation of the diaphragm and ill defined limits between liver and lungs. Pleural fluid, infiltration, and cavities with a fluid level were also frequent findings. The leukocyte counts fluctuated between 12,000 and 13,000 per cubic millimeter, never going higher, in spite of what has been reported by other observers. Endameba histolytica was found only once in the material obtained by liver puncture. It was not found in liver biopsy specimens. Treatment with emetine occasionally supplemented with chloroquine, Camoform, and antibiotics proved effective.

Diarrhea in Infancy.—At a meeting of the Academia Ecuatoriana de Medicina in December, Dr. A. Muggia of Quito reported that in a series of 379 stool cultures from infants with diarrhea pathogenic Escherichia coli were found in 40.5%. Ten serologic groups of this organism were isolated (026B6, 0127B8, 0111B4, 055B55, 0119B14, 0125B15, 0126B6, 0128B12, 086B7, and 0124B17). Of these cultures 98.5% were sensitive to kanamycin and neomycin and 56.7% were sensitive to chloramphenicol. Neomycin was found to be almost five times more effective than oxytetracycline and chloramphenicol and equally as effective as kanamycin. Diarrhea continues to be the main cause of disease and death of infants.

FRANCE

Hepatitis.—P. Mallet-Guy and co-workers (*Strasbourg méd.* 10:193, 1959) treated surgically a series of 23 patients who had chronic hepatitis and late complications of infectious hepatitis. They dissected and severed the nerve sheath surrounding the hepatic artery at the superior edge of the pancreas. This operation increased the salt and pigment contents of the bile and had a favorable effect on the glycogenetic function of the liver. The results of this periarterial neurectomy were satisfactory. Pruritus disappeared within a few hours after the operation and jaundice disappeared gradually. Cure was obtained in 16 patients. These patients' general condition was excellent when they were seen one to two years after the operation, and no dietary restrictions were required. This operation not only brought about the disappearance of jaundice but it also prevented late complications of infectious hepatitis.

Hormonal Therapy for Myocardial Infarction.—J. Bouvrain and co-workers, at a meeting of the Sociéte Médicale des Hôpitaux de Paris, reported on a series of 11 patients who had myocardial infarction and who were treated with prednisolone. Ten of these patients had had a recent myocardial infarction associated with either a state of shock or persisting fever. The other patient had had the shoulder-hand syndrome. Prednisolone was given initially in daily doses of 30 mg. by mouth. In one patient this drug was combined with hydrocortisone sodium succinate administered intravenously. This treatment caused a subsidence of fever within 24 to 48 hours in 10 of the patients, but cessation of treatment, even its gradual withdrawal, was attended by elevation of temperature in five patients between the second and the fifth day. Three patients continued to receive small doses for three weeks.

The effect on the sedimentation rate was brought about more slowly. A return to normal occurred within two weeks of treatment. In one patient who had pleuropericarditis, the pain and fever stopped within three days and the pleural effusion was rapidly reabsorbed. Diuresis with an excretion of 2 liters of urine in 24 hours was observed and was a favorable prognostic sign. Polyuria was associated in two patients with rapid disappearance of pulmonary edema, dyspnea, and roentgenologic manifestations. One unusual result of the treat-

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The items in these letters are contributed by regular correspondents in the various foreign countries.

ment was observed in a patient who six weeks after the myocardial infarction suffered from scapulohumeral periarthritis and a shoulder-hand syndrome. Proteinemia was not influenced by the treatment.

GERMANY

Chemotherapy for Pulmonary Tuberculosis.—W. Schiessle and co-workers of Freiburg (*Beitr. Klin. Tuberk.* 120:255-273, 1959) reviewed the chemotherapy of pulmonary tuberculosis. In their series 231 patients were treated with amithiozone (Thiacetazone) alone; 173 with para-aminosalicylic acid (PAS) alone; 33 with amithiozone and PAS; 53 with streptomycin, PAS, and amithiozone; 101 with various combinations of amithiozone and other drugs; 70 with isoniazid alone; 182 with isoniazid in combination with other drugs but no prednisone; and 242 with isoniazid in combination with other drugs, including prednisone. The introduction of amithiozone produced a reduction in the mortality from 40 to 4%, but cavitation was little affected. Treatment with streptomycin and the various combinations of drugs produced further improvement in the results. Isoniazid represented a marked advance, but despite great advances in chemotherapy, the ideal of complete healing of fresh tuberculous cavitation can be achieved in many cases only by surgical therapy.

Vitamins in Beer.—H. Gebauer (*Pharmazie* 4:224, 1959) stated that analysis of various types of beer showed that they have a relatively high content of vitamin B. Experiments with animals showed that a definite increase in growth, confirmed statistically, resulted when they were given small quantities of beer. Microbiological assay of beer gave the following values per liter: 9 to 700 mcg. of vitamin B_1, 140 to 800 mcg. of riboflavin, 8.5 to 23 mcg. of nicotinamide, 0.6 to 2 mg. of pantothenic acid, and 180 to 1,700 mcg. of vitamin B_6. Pasteurization produces only a slight decrease in the vitamin content. The high biological value of beer is capable of improvement by further addition of vitamin B_1.

Ganglion-Blocking Drugs for Skin Diseases.—Weyer and Röhl (*Deutsches med. J.* 10:78-82, 1959) made a therapeutic test with chlorpromazine for an average of 27 days on 238 adults hospitalized because of skin diseases associated with some autonomic imbalance (neurodermatitis, acute dermatitis, eczema, psoriasis, leg ulcers with and without diffuse dermatitis, urticaria, erythroderma, and pruritis). They gave 50 mg. of the drug three times a day initially. For most patients this was combined with 25 mg. of promethazine three times a day. The tranquilizing sedative, and the doses of chlorpromazine and promethazine, which had an antipruritic effect, were found to be valuable as supplements to the usual external applications. For some patients the dose of chlorpromazine had to be increased to 75 mg. three times a day. Syncope occurred only when patients stood up contrary to doctors' orders. Tachycardia was controlled by administration of barbiturates. No definite change in the erythrocytes was observed at the end of the test. Allergic reactions to chlorpromazine did not occur. Skin testing with the two drugs used on patients who had sudden recurrences of skin diseases produced no definite results.

Labile Hypertension.—Moeller and Heyder (*Ztschr. Kreislaufforsch* 48:413, 1959), in an effort to determine whether there is any connection between a transient rise in blood pressure and essential hypertension, analyzed a series of 2,405 patients who were treated in the hospital in 1956. Of these, 1,256 (52.2%) never had a blood pressure higher than 140/90 mm. Hg during their stay in the hospital (normotensive); 663 (27.6%) showed labile hypertension, that is, their blood pressures rose temporarily above 140/90 mm. Hg, generally in the first few days, and then fell to normal without hypotensive treatment; and 486 (20.2%) had stable hypertension (blood pressure showing fluctuations above upper limit of normal). The average age of the normotensives was 38.9 years, of the patients with labile hypertension 51.1 years, and of those with stable hypertension 58.9 years.

The age difference between the groups was assumed to represent the time taken for the labile or stable stage of hypertension to develop. Thus the difference between the average age of the patients with normal tension and those with labile hypertension (12.2 years) should be considered the asymptomatic period of essential hypertension. The development of stable hypertension from labile hypertension took, on an average, 7.8 years. This means that the course of essential hypertension, including the latent period, may be reckoned as about 20 years. The duration of the latent period may be affected by various conditions. The onset of labile hypertension may be provoked or delayed, but the total duration of the condition seems to be closely related to age. This is in accordance with the findings of Wollheim that essential hypertension is not an acquired but a constitutional disease, in which exogenous factors only determine the time of onset of clinical manifestations.

Quinine Oxydase in Diagnosis of Hepatic Disease.—H. Baier of Mainz (*Deutsche med. Wchnschr.* 84:1308-1312, 1959) stated that estimation of various serum enzyme activities is being increasingly used as a method of diagnosing liver diseases. Apart from esterases, glycolytic enzymes, especially those of the tricarboxylic acid cycle, are predominantly used. Recently the presence of quinine oxydase has been discovered in the serum of patients with hepatic disease. This enzyme is never present in normal persons or in patients with autonomic disturbances, renal disease, arteriosclerosis, or compensated cardiac disease. The critical quantity is 4 or 5 units. In patients with hepatitis the serum quinine oxydase (ChO) level indicates more exactly the degree of damage to the parenchymal liver cells than does the serum bilirubin or the serum glutamic oxalacetic transaminase (SGO-T) level, which has hitherto been generally used.

The latter fact is evident in patients with hepatitis of prolonged duration, in whom the SGO-T levels remain fairly constant, whereas the ChO level reflects every fluctuation in the course of the disease. In patients with obstructive jaundice the enzyme is absent, or present in very low concentration. If parenchymal damage occurs during obstruction the ChO level rises, but in this case the graph of the level is always a straight line, whereas in cases of hepatitis it rises to a peak and then falls. In secondary carcinoma of the liver, cholangitis, hepatic congestion, or other diseases which affect the liver incidentally, the ChO level rises in proportion to the degree or amount of damage to the liver parenchyma. In cirrhosis, the ChO level rises moderately and reaches a peak only when a fresh exacerbation of the condition occurs. Giving cortisone to patients with hepatitis causes the markedly raised ChO level to fall rapidly almost to normal, a result which can be explained only by the vasoconstrictor effect of cortisone. Quinine oxydase has the advantage, which it shares with l-phosphofructaldolase alone, of being demonstrable in the serum only if there is damage to the liver, whereas the other enzyme levels are either raised in other diseases or are normally present in serum.

Erythroderma Desquamativa.—Eckhardt and Kunad (*Kinderarztl. Praxis* 26:443-451, 1959) stated that the pathogenesis of erythroderma desquamativa is still obscure. In 95% of a series of 160 patients with this disease the onset occurred during the first three months of life. The fatality rate for this group was about 5%, much less than that observed by Lust and Pfaundler (20 to 30%). Good results were obtained with bran baths and boric acid ointment. Apart from a bland diet (ground rice and buttermilk) with vitamin supplements phenothiazine, crude liver extract, methionine, and cortisone were given. Follow-up examinations showed no evidence of a tendency to an exudative diathesis or to bronchitis and asthma.

Indications for Resection in Pulmonary Tuberculosis.—Krann and Eerland (*Beitr. Klin. Tuberk.* 119:499-515, 1959) reviewed a series of 1,496 resections performed for pulmonary tuberculosis between 1943 and 1957 (inclusive). The percentage of segmental resections rose to 84.2% while the number of pneumonectomies and lobectomies fell to 1.4% and 14.4% respectively. In the period after 1950 more than 55% of the patients showed cavitation when they were admitted. More than 70% of those who were discharged recovered after resting in bed and receiving medical treatment. At present the main indication of the need for resection is the presence of a tuberculous focus that persists unchanged in a patient who has stayed in bed and received chemotherapy over a 7-to-10-month period and who still has infected sputum and shows signs of imminent or actual development of bacterial resistance.

Follow-up investigations on those patients who were operated on showed that the primary mortality after pneumonectomy was 8%, after segmental resection 0.25%, and after combined lobectomy and segmental resection 0.6%. Preoperative and postoperative measures have undergone a marked change. In order to reduce the risk of the development of resistant strains, the right moment must be chosen for excision of the main focus. Complications included bronchial fistulas (4%) and recurrences (5.7%). After operation the results of sputum tests became negative in 97.6% of the patients, and 89.6% became completely fit for work. Of 637 patients who were followed up for more than five years, 98.1% had normal sputum and 93.8% were fit for work. Thoracoplasty was performed on some patients as a preliminary measure. There is virtually no use for intrapleural or extrapleural pneumothorax, and operations on the phrenic nerve have become obsolete.

Nontuberculous Pathogenic Mycobacteria.—G. Lebek (*Deutsche med. Wchnschr.* 13:33-36, 1959) stated that acid-fast bacilli which are not Mycobacterium tuberculosis may produce a disease similar to pulmonary tuberculosis. Lymphadenopathies in childhood that are grossly and histologically indistinguishable from tuberculosis may be produced by pathogenic mycobacteria which are not tubercle bacilli. Patients with the pulmonary form of this disease often have a dry cough but generally feel well and have no fever. Apart from this they present all the symptoms of tuberculosis. Stained by Ziehl-Neelsen's method, the organisms look like tubercle bacilli. Incubation on egg culture medium for two or three weeks gives yellow-orange colonies with a sharp edge and smooth surface. Many strains form pigment only on exposure to light. Furthermore many strains are resistant to the usual tuberculostatic drugs. They are generally pathogenic for mice and hamsters but not for guinea pigs, rabbits, and chickens. To date acute forms of the disease are unknown. The treatment of choice seems to be resection. The organisms have a low level of infectivity. It is, therefore, highly desirable that examination of cultures be made much more frequently than hitherto.

Other mycobacteria have been found which are also pathogenic to man but which are distinguishable from Myco. tuberculosis. Mycobacterium ulcerans, which gives rise to skin lesions, is one of these. It has been isolated from smears from the cement walls and the water of a fish pond. Carriers of such organisms should be separately isolated if they are treated in tuberculosis hospitals so that they do not become superinfected with tuberculosis.

INDIA

Gastric Phosphatase Activity in Cancer of the Stomach.—Ambaye and Talavdekar (*Indian J. M. Res.* 47:5 [Sept.] 1959) stated that estimations of serum acid and alkaline phosphatase levels have proved helpful in the diagnosis and prognosis of metastatic cancer of the prostate and that serum alkaline phosphatase is effective in diagnosing malignant bone tumors. Both enzymes are present in the gastric mucosa. The authors studied changes in phosphatase activity in gastric mucosa associated with malignant changes in order to observe whether these were reflected in the phosphatase activity of the gastric juice. A series of 175 randomly selected patients with various kinds of gastrointestinal disease was studied; 17 of these had histologically proved gastric carcinoma.

Studies on gastric juice showed an overlapping of values in patients with and without cancer. Four of the 17 patients with cancer showed an increase in alkaline and acid phosphatase activity and 10 showed increased alkaline phosphatase activity alone. Patients with and without cancer who had little or no phosphatase activity in the gastric juice had some free acid in the fasting sample, and those with increased phosphatase activity had achlorhydria. The increased alkaline and acid phosphatase activity seen in a few patients with normal, hyperchlorhydric, or hypochlorhydric findings after the test meal could be attributed to the absence of free acid noted in the fasting sample. Of 37 patients with achlorhydria, 30 had a raised alkaline phosphatase level and 19 had increased acid phosphatase activity. Results on achlorhydric patients were statistically significant as compared to those obtained with hyperchlorhydric, normal, or hypochlorhydric patients.

Thus the increased phosphatase activity seen in some cancer patients could be explained on the basis of achlorhydria and could not be regarded as a reliable index of malignancy of the stomach. Results of studies on normal and neoplastic gastric mucosa showed a significant increase in the alkaline phosphatase activity and a moderate increase in the acid phosphatase activity in patients with adenocarcinoma as compared to the values obtained in the adjoining uninvolved mucosa. This difference was statistically significant. The authors concluded that the changes in phosphatase activity occurring in the gastric mucosa and associated with malignancy were not truly represented by the phosphatase activity of the gastric juice. This may be due to its variable acidity and its complex composition. The phosphatase activity of the gastric juice is therefore of no diagnostic value in malignancy of the stomach.

Cholera.—*The Bulletin of the Calcutta School of Tropical Medicine* (vol. 7, no. 4, October, 1959) reported that chloramphenicol was given to a series of 79 patients with cholera. Because good results have been reported elsewhere from the use of vitamin C and antihistaminics in the treatment of uremia associated with cholera, these were also given. Fifteen patients received chloramphenicol by mouth in a total dosage of 4 Gm. in two days, and 64 received the drug intravenously in a dosage of 1 to 1.5 Gm. within 15 to 18 hours of admission. Another group of 64 patients served as controls. Stools were cultured daily. Rapid disappearance of vibrios from stools was noticed after administration of chloramphenicol by either means, the stools being vibrio-free in 48 hours. In the control group the vibrios persisted for a longer period. No adverse effects were noticed with the dosage used.

The administration of chloramphenicol did not alter the clinical course of the disease, the only difference being in the earlier disappearance of vibrios from stools in the treated group, an effect which may be important for public health. The use of vitamin C and antihistaminics did not prevent uremia, and if it developed these drugs did not promote recovery. Two types of renal damage resulted from the dehydration produced in this disease. In the first, which was reversible and was observed in most patients, functional disturbances followed a sharp fall of blood pressure and were due to renal ischemia. These patients recovered, with restoration of normal circulation. The second type was irreversible and occurred in the stage of initial shock.

Biochemical studies showed that there was little change in the initial plasma sodium and chloride level, but the initial potassium level, which was usually high, became subnormal after treatment. In view of these findings, isotonic saline solution is the ideal infusion for replacement of both fluid and salt. The degree of dehydration could be judged accurately from changes in specific gravity of the plasma. This change is mainly due to loss of fluid and should be corrected by giving normal saline solution.

Reduced Fare for Some Patients.—Patients with tuberculosis or cancer can now travel by rail for one-fourth of the normal fare to and from a hospital, sanatorium, or clinic for reexamination or a periodic check-up. Until now this reduction was available only for journeys undertaken for admission to or discharge from a hospital or sanatorium. The new concession provides that when a patient is accompanied by an attendant both parties may travel round trip on payment of a single one-way fare. Tuberculous patients can avail themselves of this reduced rate only within the state in which they reside, but no such restriction applies to patients with cancer.

UNITED KINGDOM

Maternal Influenza and Congenital Deformities.—In an investigation into the incidence of congenital deformities in Dublin, Coffey and Jessop noted that 18.4% of the mothers of abnormal babies had had influenza, but there was no epidemiologic or laboratory evidence to confirm the diagnosis. Another opportunity occurred to investigate the possible relation of maternal influenza to fetal deformities during the epidemic of Asian influenza (*Lancet* 2:935, 1959). As the onset of the epidemic was foreseen, plans for the study were prepared in advance. All women attending the antenatal clinic of Dublin's three maternity hospitals were interrogated.

There were 663 who had Asian influenza at some time during their pregnancy, and virus A was isolated in all of them by the public health authorities. These women were matched for age, parity, and ABO and Rh blood groups with pregnant women who had not had influenza. The infants born to all the women were carefully examined for congenital abnormalities, in particular, anencephaly, spina bifida, meningocele, encephalocele, hydrocephalus, and mongolism. The incidence of these in children born to women who had Asian influenza during their pregnancy was almost two and one-half times that in the control group. The anomalies were almost entirely in the central nervous system, anencephaly being the commonest. Prematurity was higher in the infants of mothers who had influenza during pregnancy, but the incidence of stillbirths was the same in the two groups. The sex of the infants was not affected by the mother's influenza.

As with rubella, the incidence of congenital malformations in the offspring of influenza victims was greater when the infection occurred in the first trimester of pregnancy. It was 7.4% in the first trimester, 4.3% in the second, and 2.0% in the third. While these figures are lower than for rubella they are serious because influenza epidemics are so common. Coffey and Jessop suggested the advisability of offering pregnant women vaccination against influenza when an epidemic is in progress or pending.

Transventricular Valvotomy.—The atrial approach to the operation of valvotomy for the surgical treatment of mitral stenosis has been widely practiced for about 12 years. The ventricular approach to the mitral valve had been suggested, but the superiority of the atrial over the ventricular route remained undisputed for several years until Logan and Turner introduced the transventricular approach to the mitral valve, which they split with a mechanical dilator. These surgeons have now reviewed their work of the last five years on 438 patients on whom this approach, which has now been widely adopted, was used (*Lancet* 2:784, 1959). The authors found that transventricular valvotomy with a dilator is quicker and more thorough than digital dilatation, even in the presence of severe calcification, with the result that the number of patients in whom division of both commissures was incomplete dropped from 26 to 11%. The rapidity of the method helped to prevent occlusion of the stenotic orifice for all but the briefest interval, and the heart was handled less because of the brevity of the procedure. There was also less risk of dislodging emboli in the atrium. The use of a stop on the dilator caused the dilatation to be gradual and thus prevented sudden rupture of the valve. The rupture occurred at the weakest point, that is, along the commissures. The dilator provided its own counterpressure, so that at no time was there any dragging on the heart. The risk of traumatic mitral incompetence was no greater than with the use of the atrial approach.

At any rate the proportion of deaths from this cause was substantially the same in both methods. The death rate in Logan and Turner's transventricular series was only 5%. It had been 6.4% in a previous transatrial series of theirs. Other advantages claimed for the transventricular operation were a more effective opening of the valve and better postoperative results. Calcification of the valve was no obstacle to the operation and was not associated with a higher mortality. The figures for cerebral embolism were slightly lower than after the atrial operation. Ventricular fibrillation was not a problem. Logan and Turner concluded that the transventricular approach and the use of a mechanical dilator was a valuable addition to the technique of mitral valvotomy.

CORRESPONDENCE

PRACTICE OF FLUID THERAPY

To the Editor:—In the article entitled "Practice of Fluid Therapy," appearing in THE JOURNAL, Sept. 5, page 131, certain statements merit discussion. With regard to rates of use of dextrose administered intravenously, the author states, "The latter is probably less than 0.3 Gm. of dextrose per kilogram of body weight per hour in the starved subject because of 'starvation diabetes'. In the hydrated, nonstarved subject, a safe figure is probably less than 0.5 or 0.6 Gm. per kilogram of body weight per hour." Wilder and Sansum (*Arch. Int. Med.* 19:311 [Feb. 17] 1917) showed that the tolerance limit of normal men and women for dextrose administered intravenously is practically constant and at a rate of about 0.85 Gm. per kilogram of body weight per hour. This is at variance with the figure of 0.5 or 0.6 Gm. given by the author.

As far as starvation diabetes is concerned, it has been demonstrated by many investigators that in normal subjects who have either been starved, kept on a low-carbohydrate diet, or kept on a diet high in fat, a diabetic type of curve may be obtained after the usual dose of dextrose is given (Sweeney: *Arch. Int. Med.* 40:818 [Dec.] 1927). It must be emphasized, however, that the elevation of the blood sugar curve is slight, indicating only a small reduction in dextrose tolerance. The conclusion may be drawn that normal persons can tolerate an infusion rate of 0.85 Gm. of dextrose per kilogram of body weight per hour. In a case in which there is a history of starvation for several days or a diet markedly deficient in both protein and carbohydrate, the maximum infusion rate is 0.7 Gm.

With regard to water balance, the author states that estimations of change in the quantity of body water are best and most accurately made by serial (usually daily) measurements of body weight. He assumes for purposes of fluid therapy that the range of daily loss of body weight as a result of negative caloric balance is about 0.1 to 0.4 kg. (4 to 14 oz.). He interprets any marked loss in weight above 0.4 kg. per day as indicating a deficiency of body water content.

The author has not taken cognizance of two important physiological principles. 1. After a subtotal gastrectomy, male patients who were maintained solely on dextrose solutions given intravenously during the postoperative period showed a five-day cumulative nitrogen deficiency of 60 Gm. and lost about 0.5 kg. (1 lb.) of body weight per day (editorial, *J. A. M. A.* 165:1830 [Dec. 7] 1957). Protein cannot be stored dry but retains with it three or more parts of water. Thus the catabolism of the 375 Gm. of endogenous protein (60 Gm. of nitrogen) resulted in the excretion of 1,125 cc. of water, with a loss of 1.13 kg. (2.5 lb.) of body weight. The loss of the 1.13 kg. of water did not in the slightest affect the water balance of the body. 2. When a patient is in negative caloric balance he does not necessarily lose weight every day. Many observers have emphasized that the curve of daily weight change is a series of ups and downs, with frequent periods of no apparent weight change. As has been repeatedly demonstrated, these irregularities are intimately associated with the storage and release of relatively large quantities of water (Newburgh and Johnston: *Ann. Int. Med.* 3:815 [Feb.] 1930). A sudden drop in weight, therefore, does not necessarily indicate that a negative water balance has developed; it may be the result of the sudden release of stored water. It may be concluded that serial daily weight measurement, as an index of water balance, is not valid in a patient with marked negative nitrogen and caloric balances.

How, then, is one to correct the marked negative water balances which result from severe diarrhea, sweating, vomiting, and loss of fluid from draining fistulas? The capacity of a normal person to tolerate parenterally administered fluid is enormous. Thus, Root and Riseman (*J. A. M. A.* 110:1730 [May 21] 1938), gave to two patients who were suffering from diabetic coma 13,800 cc. (13.8 kg. or 29.4 lb.) and 11,600 cc. of total fluid, respectively, during the first 29 hours of treatment. No sign of cardiac failure was seen in either patient. Both were fundamentally normal as regards the cardiovascular-renal system. In patients who suffer large water losses, 5 to 7 liters may be given. Recourse to weighing is unnecessary, nor need there be any concern about the diuretic action of any sugar that may spill over. Nitrogen deficit is inversely proportional to the total caloric intake. One should, therefore, give the maximum amount of dextrose in order to reduce the negative nitrogen balance.

MAX WISHNOFSKY, M.D.
615 Williams Ave.
Brooklyn 7, N. Y.

This item was referred to the author of the original article, whose reply follows.

To the Editor:—An intent of my paper was to provide rules of thumb regarding rates of dextrose infusion and interpretations of accurate serial body weights. All rules of thumb (by definition designed for average or common situations) do not take into account several contingencies. Some of these contingencies appear to be partially considered in Dr. Wishnofsky's comments.

Several investigators (references in next paragraph) extended pioneer studies (Woodyatt and others: *J. A. M. A.* 65:2067, 1915; Wilder and Sansum: *Arch. Int. Med.* 19:311 [Feb. 17] 1917) of rates of use of intravenously given dextrose in patients who require parenterally given fluids. These investigations established the variability of these rates. This variability has been confirmed by my own experience and data as well as by those of other students of fluid therapy. Occasionally nondiabetics develop significant hyperglycemia and glycosuria even with rates of infusion below 0.3 Gm. of dextrose per kilogram per hour, whereas others use practically all the dextrose given at rates of 1 Gm. or more per kilogram per hour.

One important factor which appears to account for a low rate of dextrose utilization is starvation. Thus, dextrose given intravenously at rates exceeding 0.2 or 0.3 Gm. per kilogram per hour may produce hyperglycemia and glycosuria during starvation (Winslow: *Surgery* 4:867 [Dec.] 1938; Pareira and Probstein: *Ann. Surg.* 133:299 [March] 1951). After starvation is partially corrected by the patient's use of 20 to 50 Gm. of dextrose (Pareira and Somogyi: *Ann. Surg.* 127:417 [March] 1948), an increase in rate to less than 0.5 or 0.6 Gm. per kilogram per hour will usually be tolerated. On the other hand, some patients will not tolerate this increment (Wilder and Sansum; Elman and others: *Ann. Surg.* 130:703 [Oct.] 1949; Lockhart and Elman: *Surg., Gynec. & Obst.* 88:97 [Jan.] 1949), whereas other patients can tolerate even greater increments (Wilder and Sansum; Winslow; Pareira and Somogyi; Lockhart and Elman).

Ideally, these problems are best solved by considering each patient individually and frequently estimating urinary and blood sugar levels. Short of this, reliance should be placed on such rules of thumb as I have proffered—but with full realization that exceptions to these rules do occur. Moreover, the need for an infusion rate exceeding 720 ml. of 5% dextrose solution per hour for a patient weighing 60 kg. (132 lb.) is exceptional (this rate corresponds to 0.6 Gm. of dextrose per kilogram per hour), and when this exceptional need does arise it can be met with use of more dilute solutions of dextrose plus sufficient sodium or other appropriate salts to make an isotonic solution.

Blood sugar concentrations in nondiabetics occasionally rise to values similar to those in patients with uncontrolled diabetes mellitus, as a result of excessive dextrose loading, particularly during starvation (Sweeney: *Arch. Int. Med.* 40:818 [Dec.] 1927; Conn: *Am. J. M. Sc.* 199:555 [April] 1940). Although the deleterious consequences of glycosuria, in terms of water diuresis and increased excretion of sodium chloride in already depleted patients, are well known, the fact that hyperglycemia probably entails ill-effects in itself because of its tendency to increase the osmolarity of the extracellular fluid is less well known (Seldin and Tarail: *J. Clin. Invest.* 29:552 [May] 1950; *Am. J. Physiol.* 159:160 [Oct.] 1949). This increase in osmotic pressure may then be reflected in withdrawal of water from the cells and intracellular dehydration. Proportionate dilution of extracellular fluid and reduction in the concentration of serum sodium also ensue.

The validity of my statements about serial measurement of body weight as a useful, although neglected, index of change in body water still stands. A precise correlation between serial body weight changes and changes in water balance was recently demonstrated (Paquin and others: *Metabolism* 8:16 [Jan.] 1959). This precise reflection of changes in body water content by weight measurements was observed in eight patients undergoing major gastrointestinal or genitourinary operations, irrespective of positive or negative nitrogen balance. This, and previous studies by the same group, establishes the fact that serial body weights define changes in body water content if one "corrects" for tissue loss, which comes to about 5 Gm. per kilogram per day.

My proposals in relation to serial body weights correspond closely to the opinions and data of numerous observers over the years (Newburgh and Johnston: *Ann. Int. Med.* 3:815 [Feb.] 1930; Wangensteen: *New England J. Med.* 236:121 [Jan. 23] 1947; Dieckmann and Stout: *Am. J. Obst. & Gynec.* 59:1021 [May] 1950; Moore and others: *Ann. Surg.* 141:145 [Feb.] 1955). The work of Newburgh and Johnston is particularly pertinent, because it is quoted by Dr. Wishnofsky. It is one of the early clearcut demonstrations of a close relation between body weight change and change in water balance.

Finally, a moment's reflective thinking defines certain areas in which body weight measurements are important. For example, loss of 3 liters of sweat in 24 hours will reflect itself in a loss of about 3 kg. (6.6 lb.) of weight, unless this loss has been replaced. Similarly, loss of 3 liters of unmeasured or unmeasurable fistulous, diarrheal, or other gastrointestinal fluid over 24 hours will, unless it is replaced, reflect itself in the loss of about 3 kg. in weight.

TOLBUTAMIDE

To the Editor:—I read with interest the article in The Journal, Nov. 28, 1959, page 1786, by DeLawter and co-workers. With their large group of diabetic patients, they experienced an attrition rate of 3% per month of secondary delayed failure of tolbutamide therapy after an initial success. This will come as a surprise to those who, like myself, have participated in the use of this drug from the time of its introduction in 1955. Most such patients are still amenable to treatment. The authors' findings represent an even more conspicuous discrepancy from the experience of European clinicians who have used the sulfonylureas to treat a larger group of diabetic patients for an even longer time, with a reported incidence of true secondary failure of less than 10%. Since the unwary reader might draw an unwarranted conclusion about the expected result of therapy with the sulfonylurea drugs, this unique variance from general experience deserves to be reexamined critically.

The singular experience of these workers could not be attributed to the natural progress of the disease nor to an unsual degree of dietary disregard, high even for a group of clinic patients, since the average insulin requirements of their patients after discontinuance of sulfonylurea therapy was equal to pretherapy requirements. Examination of their data, however, shows that the criteria for initial success were extremely liberal. This would have been more obvious if postprandial instead of fasting blood sugar levels had been used as the index of success. As a result, most of their patients who had good or fair success could have been reclassified as having primary failures. This is especially true in the face of such severe (judged by insulin requirements) diabetes, particularly if the classification had been made a relatively short time after starting therapy. Under such experimental conditions, secondary failure would be an inevitable outcome, given enough time. Such a significant therapeutic deficit in a group of moderately severe diabetics could lead to metabolic decompensation, with rising blood sugar levels after weeks to months and not necessarily immediately.

If, as seems probable, the above results were due to the special experimental circumstances of the study, they should not be used as a basis for general conclusions about the long-term outlook of sulfonylurea therapy in patients with diabetes without further confirmation. This is important, since the average physician treating diabetes must remain alert to possible dietary infractions and the natural progress of the disease, when evaluating therapeutic results by any means, and it would be preferable not to have his attention diverted by unwarranted or unnecessary pharmacological doubts.

Samuel B. Beaser, M.D.
31 Bay State Rd.
Boston.

THERAPEUTIC NIHILISM

To the Editor:—The "Primer on Rheumatic Diseases" which appeared in The Journal in October and November, 1959, must again be accorded a warm reception, covering as it does a broad field in such a superior manner. In an effort to contribute to the comprehensive and authoritative design which seems to prevail in this series, I should like to comment on a number of statements about the therapy of collagen diseases, which, if left unchallenged, might seem to support a pessimistic attitude toward the management of some of these diseases.

The discussion on polyarteritis nodosa, under the section on treatment (*J. A. M. A.* 171:1355 [Nov. 7] 1959), begins with the statement "No specific therapy is known." Again, the section on the treatment of dermatomyositis starts with the words, "Therapy is largely symptomatic." Both discussions of treatment include qualified statements concerning the virtues of corticosteroids in therapy. Judging by the literature, therapy of dermatomyositis with corticosteroids has been of value in only a few patients so treated. Yet, as the Primer states, enough instances of striking improvement have occurred to justify their continued use. Pollock reported a patient with dermatomyositis in whom ethylenediamine tetraacetic acid sodium was used with apparent benefit (*California Med.* 90:284 [April] 1959) and Zarafonetis (*Texas J. Med.* 49:666 [Sept.] 1953) reported a series of patients who improved significantly while treated with potassium para-aminobenzoate.

In polyarteritis nodosa the picture appears somewhat brighter. Schick (*M. Clin. North America* 42:959 [July] 1958), reported a series of 50 patients treated with corticosteroids, on 30 of whom follow-up data were available. In 21 of these the disease appeared to be in remission or adequately suppressed when they were last seen. A series of three children who responded well to treatment with cortisone or ACTH was reported by Yonis (*Ann. paediat.* 192:65 [Feb.] 1959; abstracted in *J. A. M. A.* 170:1476 [July 18] 1959). A series of patients treated with cortisone as reported to the British Medical Research Council (abstracted, *J. A. M. A.* 164:922 [June 22] 1957) appeared to do much better than a control group. Another optimistic report was abstracted in The Journal (165:1319 [Nov. 9] 1957).

As for scleroderma the Primer states that no specific remedies have appeared to be of consistent value in the treatment of this disease. By and large, this is true, yet, to accept this statement without reservations would be to deny some patients benefits which have been reported after specific therapy for specially selected patients with scleroderma. Talbott and Moleres Ferrandis (Collagen Diseases, Grune and Stratton, New York, 1956, p. 176) in discussing the treatment of scleroderma give much credit to steroids for the symptomatic benefit they produce. Winkelmann (*Proc. Staff Meet. Mayo Clin.* 34:55 [Feb. 4] 1959) found that relaxin, chelating agents, and steroids produced some beneficial effects in selected patients with scleroderma, effects which in some patients were transient and in others difficult to evaluate. Another agent considered effective in the treatment of this disease is potassium para-aminobenzoate, as reported by Zarafonetis (*Ann. Int. Med.* 50:343 [Feb.] 1959; *Texas J. Med.* 49:666 [Sept.] 1953).

Thus, granted that there are various limitations and reports of failures in treatment, nevertheless, a variety of agents is available for therapy of the diseases mentioned, and these are effective enough to justify the maintenance of an expectant, rather than a pessimistic, attitude toward the results of treatment.

George X. Trimble, M.D.
Director of Medical Education
Seaside Memorial Hospital of Long Beach
Long Beach, Calif.

SUM RITIN

Dear Mr. Editur:—jest read a peice of Dr. Sam's riting [Garlan, S. A.: Rebirth of General Practice, *J. A. M. A.* 171:1941 (Dec. 5) 1959.] in last weaks Journal bout doctoring in the wilds of Montana. I kinda took it to hart cause I'm one of them there Doc's that confines my doctoring to what you Eastern fellas call Internal Medicine. Thought you might like to know, Dr. Sam, that we also have Docs that kinda confine their doctoring to kids, delivering babies, broken bones, cutting, and even nerves. A right good number of these Docs, Dr. Sam, have had the gumption to leave the old homestead to take and pass some of those Eastern Board Exams. These Docs do a right proud job of doctoring and sure do see a heap of folks. We have a good many General Docs out here too and they're right nice fellas and do an awful good job. Hope these few remarks kinda clear the air, Partner. Much obliged.

E. J. Scherba, M.D.
110 Neill Ave.
Helena, Mont.

P. S. Woulda rote more, Dr. Sam, but have to go down the road a peice and give a dose of salts to a case of alpha 3-Globulinemia. If you have any idees on this here condition I would surre be tickled pink to here from you. Please stop by and meet ma and the younguns if you ever visit Montana.

The invitation is appreciated.—Ed.

COLLECTING BOTTLE FOR T-TUBES IN AMBULANT PATIENTS

To the Editor:—I am sure most surgeons who perform common bile duct surgery have had difficulty obtaining a satisfactory collecting bottle for the T-tube in an ambulant patient. For the past four years I have been using a Fleets enema bottle and it has given better results than any other type of bottle I have ever used. I usually have the nurses empty the bottle and give the enema solution to any patient who may need an enema. This leaves an excellent collecting bottle to attach to the end of the T-tube and tie on to the dressing or binder. It has the advantages that (1) the enema tip will accommodate almost any size of T-tube, (2) it is plastic and will not break, (3) it is soft and comfortable for the patient, (4) it is not as heavy as an ordinary glass bottle, and (5) the top remains tight, yet it is easily removed for cleaning.

W. G. Cauble, M.D.
Suite 102
Doctors' Building
Wichita, Kan.

CARPAL TUNNEL SYNDROME

To the Editor:—In The Journal, Nov. 14, page 1625, in Questions and Answers, there is an inquiry about the carpal tunnel syndrome. The question posed was that of the relationship of carpal tunnel syndrome to systemic diseases. The answer to this question was misleading. An article entitled "Systemic Disease and the Carpal Tunnel Syndrome" by Grokoest and myself that appeared in The Journal, June 12, 1954, page 635, should answer Dr. Jabush's question.

Felix E. Demartini, M.D.
620 W. 168th St.
New York 32.

To the Editor:—I would like to comment on the question submitted by Dr. Jabush on the association of carpal tunnel syndrome to systemic disease, appearing in Questions and Answers in The Journal, Nov. 14, 1959. I disagree with the answer that systemic disease is not found in patients exhibiting this syndrome. In a personally studied case (with Dr. William Dameshek), the syndrome appeared in a patient who had had multiple myeloma for about two and one-half years. The median nerve compression was relieved neurosurgically. At the time of the operation material removed from the patient's wrist was found to be "amyloid." While I do not have the exact reference to this association, I do recall an abstract which appeared in *Modern Medicine*, probably in 1957, in which several patients with amyloidosis, both primary and secondary, in whom carpal tunnel syndrome was present, were described.

Fernando Rubio Jr., M.D.
501 11th St. N.
St. Petersburg 5, Fla.

I am pleased to discover that Questions and Answers are widely read.—Ed.

MEDICAL FILM REVIEWS

Technique with the Fresh Temporal Bone: 16 mm., color, sound, showing time 17 minutes. Prepared in 1958 by Harold F. Schuknecht, M.D., Detroit. Procurable on loan (service charge $3) from Motion Picture Library, American Medical Association, 535 N. Dearborn St., Chicago 10.

In the technique shown at autopsy, the oscillating circular Stryker saw is used. The brain is removed first and then the bone plug cutter, 1.5 in. in size for the adult, is centered on the arcuate eminence. After the bone plug has penetrated the base of the skull, the plug is grasped with bone forceps and removed. If the specimens are to be used for future anatomic-surgical dissection, they may be preserved by refrigeration. The fresh state may be preserved for many months by placing the specimens in moist cotton, wrapping them in freezer paper, and placing them in a deep freezer. For anatomic-surgical dissection, the temporal bones are placed in a special temporal bone holder which consists of a heavy hemispherical bowl held in a stand which permits it to be tilted. If the temporal bones are acquired from a person having deafness or vertigo, they are placed in fixative immediately and then decalcified, embedded in celloidin, and serially sectioned. The acquisition of fresh human temporal bones is essential to otological training and research programs. This is an excellent teaching film. The technique shown is an improvement on the older methods of removing the temporal bone, both from the point of view of ease of removal and the fact that this technique does not increase the technical problems of the mortician or affect the external appearance of the body. This film is recommended for otolaryngologists, residents, and pathologists who may be interested in removing temporal bones at autopsy for histological study or in anatomic dissections.

Technique of Biceps Cineplasty: 16 mm., color, sound, showing time 30 minutes. Produced in 1958 by and procurable on loan from Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington 12, D. C.

This is an excellent film on the operative technique of biceps cineplasty. It goes into minute detail of the meticulous surgical technique used in this procedure. Positioning of the patient, positioning and outlining the flap, and dissection are illustrated. The flap is folded into a tube and drawn through the tunnel in the perforated biceps muscle, the corners are closed, and the defect is covered with a split-thickness graft. The progress of the wound healing and the physical therapy program for developing the biceps muscle are shown. Also demonstrated is the training program in the use of prostheses. Rehabilitation is aimed at development of use of the prosthetic hook and hand in everyday activities. The photography of the surgical technique is good. Narration is clear, with ample explanation of the demonstrations. Postoperative scenes are used effectively. The film will be of particular value to the general and orthopedic surgeon who deals with the amputee.

NEW FILM ADDED TO A. M. A. MOTION PICTURE LIBRARY

Medifilm Report of the 13th Annual Clinical Meeting: American Medical Association, December 1-4, 1959, Dallas, Texas: 16 mm., black and white, sound, showing time 25 minutes. Presented by the American Medical Association and Schering Corporation. Produced in 1959 by Fordel Films, Inc., New York. Procurable on loan (no service charge) from Motion Picture Library, American Medical Association, 535 N. Dearborn St., Chicago 10, and Audio Visual Department, Schering Corporation, Bloomfield, New Jersey.

This film was prepared as a service to physicians who were unable to attend the meeting. Physician interviews, panel discussions, special guest lectures, and scientific exhibits are featured in this documentary film. J. S. Chapman, member of the Dallas County Medical Society, host organization, is narrator. Some selected highlights of the meeting include an interview with H. Strughold, professor of space medicine, Randolph Air Force Base, Texas; a discussion by S. G. Wolf on use and abuse of tranquilizers and their role in psychiatric care; a panel discussion on treatment of rheumatoid arthritis with W. P. Holbrook, chairman, M. Ziff, C. J. Smyth, and W. S. Clark; and an illustrated lecture by O. Auerbach concerning his recent findings on the trachea and bronchi of smokers. The narrator interviews various exhibitors as the camera focuses on their scientific exhibits. B. E. McLaughlin discusses emotional disturbances; J. Q. Gant Jr. points up aspects of his exhibit on griseofulvin in ringworm infections; N. O. Rothermich explains use of latex fixation tests for rheumatoid arthritis; and E. L. Becker discusses the use of percutaneous renal biopsy in establishing tissue diagnosis of nephrotic syndromes in adults and presents a brief outline of treatment procedures.

Typical Dallas scenes provide a colorful background. The film offers a dramatic sampling of convention highlights and a glimpse of the convention city, giving the viewer a sense of participation. It summarizes some outstanding scientific subjects which were presented and discussed before a large group of inquiring physicians. The photography and sound recording in this film are well done, and it is highly recommended to state and county medical societies, hospital staffs, and individual practitioners. Medical students, interns, and residents will also find items of interest.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Unexplained Heart Failure in the Aged. G. A. Rose and R. R. Wilson. Brit. Heart J. 21:511-517 (Oct.) 1959 [London].

When older persons die of heart failure, the clinician generally assumes that myocardial ischemia is a factor, but sometimes the pathologist can neither confirm this diagnosis nor suggest any other adequate explanation. The authors collected data on such cases in the hope of clarifying their etiology. Their study was based retrospectively on 50 consecutive autopsies on patients who died, at an age of 70 years or more, of heart failure for which the clinician could find no adequate explanation. A proper assessment of the importance of various common conditions—hypertension, coronary disease, and brown atrophy, for example—required some standard by which to estimate their general incidence in the elderly. Each heart failure subject was, therefore, matched by the next person of the same sex and age (± 3 years) who came to autopsy without evidence of heart failure, and also without any of the clinical conditions specified earlier as possible causes of heart failure.

It was found that chronic failure of a structurally normal heart was common, and the authors do not consider it unreasonable to postulate that they may be dealing with a myocardium that has been weakened through some process connected with age itself. The pathologist, by examination of the heart alone, cannot tell whether a patient has died of heart failure. Campbell has taught for years that he cannot distinguish between 2 large hearts, both from patients with hypertension, one of whom has died after a road accident and the other after congestive failure. Inasmuch as one is already familiar in the aged with the paradox of failure of the mind and weakening of the limbs which are not reflected after death in any visible change in the brain or muscles, a similar obscure weakening may also affect the myocardium. Nevertheless, such a hypothesis must not be too readily adopted, lest it hide some cause of myocardial failure more specific than mere senility.

On the basis of the autopsy findings, the authors feel that their patients can probably be divided into 3 etiological groups: (1) those with former hypertension; (2) those with occult myocardial ischemia; and (3) those with normal blood pressures and with hearts of normal appearance. This last entity can perhaps be referred to as "senile heart failure," provided one recognizes that the term "senile" is purely descriptive and does not necessarily imply the absence of any more specific underlying cause. It is disappointing that this analysis has indicated no means of distinguishing in life between these very different types of cases. This difficulty, however, serves as a warning against the diagnosis of myocardial ischemia in all cases of clinically obscure heart failure in the aged. Auricular fibrillation, which was common in all the etiological groups and also among the control subjects, did not appear to be related to coronary disease.

The Pathogenesis of Infarction of the Right Ventricle. W. G. Wade. Brit. Heart J. 21:545-554 (Oct.) 1959 [London].

It is rare for the right ventricle to be predominantly affected in myocardial infarction, the relative involvement of this ventricle in 2 large series being 1.7 and 3% respectively. In this paper there are presented the pathological and clinical features of 11 new cases of right ventricular infarction, the records of which were obtained from the Institute of Pathology of the University of Belfast. This constitutes the largest series of cases of this kind which has so far been published. Histological material was available in each case. For comparison, the corresponding gross pathological features in a consecutive series of 100 cases of left ventricular infarction investigated in this institute were also assembled.

The author concludes that extensive infarction of the right ventricle is usually a direct result of an occlusion of the right coronary artery. Earlier occlusive lesions occurring in the anterior descending branch of the left coronary artery probably play a considerable role in the pathogenesis of this type of infarct. Since the right coronary artery is usually the dominant vessel on the posterior cardiac wall, there is frequently an extension of the infarct to the posterior interventricular septum and adjoining portion of the left ventricle. It is

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The place of publication of the periodical appears in brackets preceding each abstract.

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suggested that it is this extension of the lesion, rather than the involvement of the right ventricle itself, that contributes to the high incidence of circulatory failure in these cases. Extension of the infarct to the right atrium is also relatively common. There is evidence suggesting that pulmonary hypertension plays an etiological role in right ventricular infarction. When the thin-walled right ventricle becomes infarcted, the lesion is particularly liable to become transmural; hence, rupture, pericarditis, mural thrombosis, and pulmonary embolism are frequent attendant lesions.

The histological features of right ventricular infarction closely resemble those of left ventricular infarction. Without the assistance of an electrocardiogram including right precordial leads, there is little chance of achieving a precise clinical diagnosis. The prognosis in patients with right ventricular infarction tends to be poor, and the increased risk of pulmonary embolism makes the use of anticoagulant therapy imperative, although the tendency for hepatic insufficiency to develop necessitates great care in its use. Several physiological factors acting through the intercoronary collateral circulation are enumerated as being responsible for the relative immunity of the right ventricle to infarction.

Acute Benign Pericarditis and the Coxsackie Viruses. R. L. Gillett. New England J. Med. 261:838-843 (Oct. 22) 1959 [Boston].

The author presents clinical and laboratory data on 4 patients with the syndrome of acute benign pericarditis, who were among active-duty personnel stationed at the United States Naval Air Station, Jacksonville, Fla. Evidence of appreciable levels of antibody titers to the Coxsackie virus, group B, type 5, was demonstrated in the serum of the 4 patients. The stools were negative for the virus in 2 patients. One of these 4 patients was symptomatic for about 2 months, with persistence of a pericardial friction rub for about 10 weeks after the onset of symptoms. Another patient was symptomatic for about 10 weeks, and the pericardial friction rub was audible up to the 11th week of illness. Strict bed rest seemed to be an important factor in the treatment of these patients; salicylates proved helpful in relieving their symptoms and reducing fever. The indications for the use of salicylates should be similar to those in acute rheumatic fever.

Before it is suggested that a clinical syndrome represents a disease caused by a Coxsackie virus, the patient should be given an adequate clinical examination. The clinical syndrome should be one of previously undetermined etiology, not associated with, or related to, known pathogens. Antibody response to a virus of the Coxsackie group should be demonstrated coincident with the patient's illness. Virological and clinical evidence of poliomyelitis should be excluded. Least important, the Coxsackie virus should be recovered from the patient. Findings in the patients of this study give further evidence that the Coxsackie viruses may well be a major cause of the syndrome of acute benign pericarditis.

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery in an Adult. J. M. George and D. M. Knowlan. New England J. Med. 261:993-996 (Nov. 12) 1959 [Boston].

The 14th case of the anomalous origin of the left coronary artery from the pulmonary artery in an adult is reported; data on the 13 previously described cases are tabulated. In the 26-year-old woman whose history is presented, the anomaly was associated with rheumatic heart disease, a combination not previously described. Despite the presence of rheumatic heart disease with mitral insufficiency, cardiomegaly, and severe congestive heart failure, this patient survived to adult life with an anomalous origin of the left coronary artery from the pulmonary artery. The sudden death, which could have been attributed to many factors associated with rheumatic heart disease, is a common feature of an anomalous left coronary artery in adults. The vein-like appearance of the left coronary artery at autopsy suggests that the coronary supply of the myocardium in these patients is derived from the right coronary artery and that blood flow in the left coronary artery is toward the pulmonary artery instead of away from it.

Many surgical procedures have been suggested. Paul and Robbins advocated placing talc in the pericardium to increase blood flow to the myocardium. Others have recommended producing pulmonary hypertension and thus increasing perfusion pressure in the anomalous coronary artery. A transplantation of the portion of the pulmonary artery that contains the anomalous coronary artery to the aorta has also been suggested. Recently, Case and associates described a method of surgical correction, based on the fact that flow in the anomalous coronary is toward the pulmonary artery. They suggested ligation of the aberrant vessel at its origin; this converts the anomaly into a single coronary artery. They mentioned 3 infants who had been subjected to this procedure. As yet, no adult patients have undergone surgery.

Congenital Kinking of the Aortic Arch. J. N. Pattinson and R. G. Grainger. Brit. Heart J. 21:555-561 (Oct.) 1959 [London].

In the past few years a congenital anomaly of the aortic arch—a kinked or buckled arch—has been described and established as an entity. Although it usually presents a characteristic roentgenologic picture, it is not as yet widely recognized by either radiologists or clinicians. In this anomaly the descending portion of the aortic arch is acutely kinked, with an angular convexity directed forward, downward, and slightly to the right at the level of the ligamentum arteriosum. The kink occurs at the aortic isthmus, where there is normally a faint indentation on the concavity of the aortic arch immediately proximal to the slight dilatation (aortic spindle) of the upper descending aorta. The aorta proximal to the kink is elongated and rises higher in the mediastinum than usual. The ascending aorta is not dilated and is normally situated. The apex of the abnormal kink is closely applied to the upper and posterior aspect of the left pulmonary artery and left main bronchus, which may be displaced forward, downward, and to the right. The esophagus is also usually displaced forward and to the right, since it is closely applied to the kinked segment. The aorta immediately distal to the kink may be dilated. It turns sharply backward and slightly to the left, curving downward into a normally placed descending aorta.

The authors describe 5 new cases of kinked aortic arch without coarctation. The roentgenologic appearance of this anomaly is described in detail, not only from the posteroanterior but also from several other views. Thirty-seven cases of kinked aortic arch without coarctation have been previously reported or referred to. The abnormality is more frequent than this figure suggests; the authors have knowledge of, or have seen, several other patients not included in this series. The roentgenologic diagnosis is important, because otherwise the patient is frequently subjected to complicated, unnecessary, or uncomfortable procedures, such as angiography or even exploratory thoracotomy. The correct recognition is of practical importance to avoid the mistaken diagnosis of mediastinal tumor.

The Latex-Fixation Reaction in Nonrheumatic Diseases. E. Dresner and P. Trombly. New England J. Med. 261:981-988 (Nov. 12) 1959 [Boston].

The serum agglutinating factor for amboceptor-sensitized or FII (fraction II)-coated erythrocytes and latex particles is still thought to be specific for rheumatoid arthritis and closely allied diseases, and the variable occurrence of positive reactions in control subjects has not been satisfactorily explained. The incidence of these so-called false-positive reactions in serums from normal subjects and patients with nonrheumatic diseases varies in different reports from less than 1% to as high as 30%. This investigation represents a systematic attempt to delineate the conditions, other than rheumatic diseases, that regularly cause agglutination of FII-coated latex. Single and repeated samples of serum were obtained from 140 apparently normal subjects, 258 subjects with rheumatoid arthritis, connective-tissue diseases, and other rheumatic disorders, and 404 subjects with a variety of nonrheumatic diseases. Latex-fixation tests were performed on whole serums and on reconstituted euglobulin fractions by the inhibition-bloc technique of Ziff and collaborators, which was slightly modified. The merit of the inhibition-bloc technique as applied to sensitized erythrocyte and FII-coated latex systems lies in its great delicacy in detecting agglutinating activity in rheumatoid arthritis, but unfortunately this is not accompanied by a parallel increase in specificity of the reaction, even for the group of connective-tissue diseases as a whole.

The authors arrive at the conclusion that, when a sensitive inhibition-bloc technique is used, the latex-fixation test of Singer and Plotz is found not to be specific for rheumatoid arthritis. In addition to the connective-tissue group of diseases, positive reactions are consistently found in active hepatocellular diseases, the acute and convalescent phases of viral infections, seropositive syphilis, and some hyperglobulinemic states. The factor common to these conditions, and responsible for the latex fixation, is a circulating macrogamma globulin, which combines, probably in a nonspecific way, with the FII reactant coating the latex. The reaction is competitively inhibited by an excess of normal, low-molecular-weight gamma globulin. Latex fixation does not take place in the presence of abnormal gamma globulin of low molecular weight as in myelomatosis. Although they share some common physical properties, such as their molecular size, electrophoretic mobility, and ability to agglutinate FII-coated latex, pathological macroglobulins are probably not identical in other respects.

The Protean Manifestations of Histoplasmosis as Illustrated in Twenty-Three Cases. F. G. Conrad, S. Saslaw and R. J. Atwell. A. M. A. Arch. Int. Med. 104:692-709 (Nov.) 1959 [Chicago].

The authors report on 23 patients with histoplasmosis—6 from the Ohio Tuberculosis Hospital and 17 from the Ohio State University Hospital in Columbus—who presented diagnostic problems with a variety of manifestations. There were 13 men and 6 women, between the ages of 18 and 74 years, and 3 boys and 1 girl, between the ages of 3 and 11 years. Seven patients had acute disease resembling common respiratory infections. Of these, one died after dissemination of the disease, 2 required pulmonary resection, and in the others the condition cleared spontaneously with only symptomatic care. Ten patients had chronic, debilitating pulmonary disease resembling tuberculosis. Seven of them were treated for tuberculosis, and in 2 the presence of concomitant Mycobacterium tuberculosis was revealed by culture. Four of the patients with chronic histoplasmosis had exacerbations and remissions during the course of their illness. One patient had multiple arthralgias associated with weakness. He was thought to have sarcoidosis because of the granulomas which were seen in a liver biopsy specimen. This patient made a complete recovery on a regimen of modified rest alone. One patient presented as a typical case of hypersplenia; she had none of the usual symptoms of histoplasmosis and died of cerebral hemorrhage secondary to a thrombocytopenia. At autopsy, miliary involvement of spleen, lung, lymph nodes, and bone marrow was observed.

The treatment of histoplasmosis is mainly supportive. Surgery may be indicated for single localized lesions. Amphotericin B administered intravenously shows promise, but because of its side-reactions should be reserved for selected patients who show progression of the disease on symptomatic treatment and bed rest.

Late Progression of Pulmonary Coccidioidomycosis. M. J. Small. A. M. A. Arch. Int. Med. **104**:730-740 (Nov.) 1959 [Chicago].

The author reports on 4 men, between the ages of 25 and 52 years, with pulmonary coccidioidomycosis, who were admitted to the Veterans Administration Hospital in East Orange, N. J., in the past 2 years, and whose clinical course was strikingly different from that commonly accepted. In the first patient, the exposure to infection with Coccidioides immitis presumably occurred during Air Force service in Tucson, Ariz., in 1954 and early 1955, but was not clearly evident on a chest roentgenogram obtained at the time of discharge in February, 1955. In July, 1955, however, a coccidioidal cavity was present, and the clinical findings and those in the specimen of pulmonary segmental resection suggested that there was a bronchogenic seeding of the left lower lobe and pleura from this cavity and the subsequent surgical intervention respectively. In the second patient, there were a documented single exposure during Army service in Arizona, in an area endemic for coccidioidomycosis, in 1943; a negative chest roentgenogram obtained from the patient in 1946; a visible lesion on a chest roentgenogram obtained in 1951, slowly increasing in size by 1958; and clinical, skin test, and pathological findings in a lymph node biopsy, all of which pointed to a diagnosis of pulmonary coccidioidomycosis. In the third patient, a negative chest roentgenogram was obtained on induction into the Army in 1951, and a lesion appeared on a routine chest roentgenogram obtained in 1954 while the patient served in the Army in Arizona. This lesion remained stable for about 2 years but then showed evidence of a spread to the contralateral lung. The spread cleared while the patient was taking streptomycin and isoniazid, but a left apical lesion went into frank excavation and proved to be a coccidioidal cavity. In the fourth patient, a nodular lesion appeared in a chest roentgenogram obtained from the patient in 1945 when he was discharged after a 3-year Army service in western Texas. The appearance of this lesion did not change from 1945 to 1949, but there was a striking increase between 1949 and 1957, during which period the patient was not followed by chest roentgenograms. All smears and cultures proved to be negative for tubercle bacilli; tuberculin skin tests were negative; but the coccidioidin skin test was positive, and the resected specimen revealed a clean-walled cavity, the appearance of which was compatible with coccidioidomycosis.

These findings indicate that pulmonary coccidioidomycosis, contrary to the commonly held current concepts, may be a disease which does not manifest itself until a prolonged period after exposure in the endemic area, which may undergo late, continued, slow progression over a period of years, and which may spread by the bronchial route from cavities previously considered benign to produce infiltrations years later in the lung, indistinguishable by x-ray from those of exudative tuberculosis. Since these 4 cases were observed in persons residing in the East, whose x-ray manifestations of disease were not observed until from 5 months to many years after their documented residence in a known endemic area for coccidioidomycosis, it would appear that late pulmonary manifestations of coccidioidomycosis must be added to the list of differential diagnoses when considering stationary or progressive coin lesions, cavitary lesions without positive bacteriological findings for tuberculosis, and parenchymal infiltrations resembling tuberculosis, even years after exposure in an endemic area. Carefully taken histories eliciting residence in the endemic area, as well as the performance of the coccidioidin and tuberculin skin tests, have been the most helpful factors in leading to a positive diagnosis of late, active, pulmonary coccidioidomycosis in these patients. With the increasing tendency toward vacations by flight to the Southwest, it is felt that physicians in all areas of the United States must be alert to the possibility of this disease.

Disseminated Cryptococcosis Producing a Sarcoid Type Reaction: The Report of a Case Treated with Amphotericin B. L. H. Shields. A. M. A. Arch. Int. Med. **104**:763-770 (Nov.) 1959 [Chicago].

The author reports on a 42-year-old woman who had been working on a farm in North Carolina until she was admitted to the Harrisburg (Pa.) Polyclinic Hospital for incapacitating pain and swelling in the left shoulder, hip, and ankle, profuse sweating, frontal headaches, chills, fever, and loss of weight. The patient thus showed the picture of polyarthritis. The roentgenographic findings demonstrated that the disease was not limited to the joints, but was generalized. A clavicular biopsy showed cells suggestive of lipid granulomatosis, and a biopsy of a lymph node from the right axilla was consistent with sarcoid. The draining sinuses, lack of bacterial cause for the purulent exudate, septic course, multiple areas of involvement, and nonspecificity of pathological data suggested that a fungus was the causative agent. Appropriate studies resulted in positive cultures for cryptococci from a left supraclavicular abscess, from an osteolytic lesion in the external malleolus of the left fibula, the sternal marrow, and the spinal fluid. Mycotic organisms appearing as budding capsules, staining with mucicarmine, were identified. The diagnosis of cryptococcosis was indisputably established, although many of the aspects of the disease pattern suggested sarcoidosis.

Clinical remission was induced by slow infusion over 6 to 8 hours of amphotericin B; the patient received 2 courses with 54 therapeutic doses of the drug, totaling 3,162 mg., or about 45 mg. per kilogram of body weight. Dilution of the drug was effected to 1 mg. in 20 cc. of 5% dextrose in water. Laboratory evidence of drug toxicity of an acute nature was limited to a rise in blood urea nitrogen level after each infusion. The urea level was controlled when it reached 35 mg. per 100 cc. by omitting treatment for 1 or 2 days. Long-term laboratory toxic effects were difficult to separate from the effects of the patient's disease. There was a constant drop in hemoglobin level during both courses of therapy, not explained by bone marrow suppression or by hemolysis. The low white blood cell count with slight eosinophilia seemed to be related to the drug administration. There was a definite drop in serum potassium level during both courses of treatment.

Laparotomy 13 months after the institution of therapy showed involvement of the liver, spleen, and regional lymph nodes by a typical sarcoid-type reaction. Cryptococcic organisms were found in some of the granulomas. The clinical status of the patient in remission was indistinguishable from that seen in typical Boeck's sarcoidosis. It is believed that the widespread sarcoid-type reaction observed represents an immune response to primary cryptococcic invasion. The case of this patient is unusual in that the infective cryptococci have not only been associated with sarcoidosis, but have actually been observed in the area of sarcoid-type response, supporting the concept that the sarcoid reaction may be caused by various causative agents.

Porphyria Cutanea Tarda: Report of a Case Effectively Treated With Dimercaprol (BAL). A. G. Redeker, R. E. Sterling and B. Archer. A. M. A. Arch. Int. Med. 104:779-782 (Nov.) 1959 [Chicago].

The authors report on a 47-year-old man with "symptomatic" porphyria cutanea tarda, who was admitted to the Los Angeles County General Hospital in 1958. The skin of the patient's face, neck, and arms had an obvious dusky, violaceous hue, and he had mild hypertrichosis of the forehead. Numerous vesicles and reddish-black crusts were present on the face, neck, ears, arms, and hands. The ears were grossly edematous and oozed a clear fluid. There were a few shallow ulcers, a few large bullae, and many depigmented scars on the hands and forearms. There was no jaundice, and neither the spleen nor the liver could be palpated. The urine was of a burgundy color and contained large amounts of porphyrin. The patient's temperature on admission was 103 F (39.5 C). The patient was treated with bed rest, salicylates, and moist compresses applied to the ears. Two days later the temperature was restored to normal, and the patient appeared less toxic. But the urinary porphyrin excretion remained high, and new skin lesions continued to form. Dimercaprol was then administered in doses of 300 mg. per day for 4 days. Concurrent with the institution of this therapy, new skin lesions ceased to appear, and there was rapid healing of the preexisting ulcers and bullae. Two weeks after the patient's discharge from the hospital a few new bullous lesions had appeared on his hands, and the urinary porphyrin excretion had returned almost to pretreatment levels. Treatment with dimercaprol was then reinstituted, 150 mg. 2 times a week, and was continued for the following 3 months. During this period evidence of cutaneous photosensitivity was totally lacking, although very mild skin fragility persisted. The total porphyrin excretion was restored almost to normal.

The rapid clinical improvement resulting from dimercaprol therapy was accompanied by a decrease in both urine and fecal porphyrin excretion. Both abnormal sulfobromophthalein retention and a decreased serum protein level, present during relapse, became normal after dimercaprol therapy, emphasizing the role of hepatic dysfunction in patients with porphyria cutanea tarda. Treatment of this disease with dimercaprol is both safe and effective.

The Nephrotic Syndrome: Renal Biopsy Findings in Adults Responding to Prednisone. A. R. Sharpe Jr. and A. M. Unger. A. M. A. Arch. Int. Med. 104:684-691 (Nov.) 1959 [Chicago].

The authors report on 6 men and 2 women, between the ages of 24 and 41 years, with severe nephrotic syndrome, the clinical diagnosis of which was based on the presence of massive edema, heavy albuminuria ranging from 6.2 to 16 Gm. per day, and hypoalbuminemia ranging from 0.6 to 1.5 Gm. per 100 cc. The value of renal biopsy in the diagnosis and management of the nephrotic syndrome appears well established. Percutaneous renal biopsy, therefore, was performed on all the patients, and the outstanding pathological lesion in 6 of the 8 patients was thickening of the basement membrane. The biopsy findings were nearly normal in one patient. The absence of dilated, atrophic, or scarred tubules in all the patients was notable and of value in ruling out a chronic destructive process. No significant changes in the renal vessels were apparent, ruling out chronic renal-hypertensive disease.

When renal biopsy in adult patients with the nephrotic syndrome shows nearly normal glomeruli or generalized thickening of the basement membrane, it appears reasonable to institute a regimen of steroid therapy. These patients were treated intensively with prednisone at the Medical College of Virginia Hospital and the McGuire Veterans Administration Hospital in Richmond; 60 mg. of the drug per day in divided doses was given for the first 3 days of each week. Each month the dose was decreased by 5 mg. a day in order that at the end of one year the patient would have finished his treatment program. Diuresis to dryness was observed in every patient after the initial course of therapy. Proteinuria disappeared in only 2 patients. The remaining 6, while still excreting only small quantities of protein, were free of edema. Serum albumin concentration increased and serum cholesterol level decreased markedly after treatment. The blood urea nitrogen level remained essentially unchanged, except in one patient in whom there was a marked reduction. With the use of 60 mg. of prednisone per day, no serious complications occurred. "Moon face" appeared in 4 patients, and acne developed in 1. In none of the patients was it necessary to discontinue steroid therapy. Any conclusion as to the beneficial effects of this therapy must be drawn in the light of the natural history of the disease, as it is characterized by exacerbations and remissions. However, with the exception of one patient, all these patients had been continuously edematous for more than 3 months preceding the treatment, supporting the impression that the course of the disease was positively affected by steroid treatment.

Cardiovascular Disease Among Physicians. N. Reitman. J. M. Soc. New Jersey 56:673-676 (Nov.) 1959 [Trenton].

A questionnaire concerning the incidence of hypertension, obesity, stress and strain, diet, and diabetes in association with cardiovascular diseases was sent to 427 physicians in New Jersey. This sample group was selected at random, taking every 11th physician listed in the state. Two hundred sixty replies were received, 247 from male and 13 from female doctors. There were 25 cardiacs (10%) and 235 noncardiacs (90%). The cardiovascular diseases were rheumatic in 3 respondents, hypertensive in 7, arteriosclerotic in 13, aortic coarctation in 1, and thyrotoxic disease in 1. Hypertension was present in 28% of the 25 cardiac physicians, obesity in 10%, stress and strain in 92%, dietary restriction in 52%, and diabetes in 8%. In the noncardiac group the frequencies were: hypertension in 8%, obesity in 48%, stress and strain in 97%, dietary restriction in 34%, and diabetes in 1%. It appears that hypertension and diabetes are statistically significant factors in the incidence of cardiovascular disease in this sampling of New Jersey physicians.

Comparing the data obtained in this survey with the results of other studies on the subject, the author also concludes that mortality from heart disease among physicians in New Jersey is almost exactly the same as in the rest of the United States. There is a statistically significant increase in physician mortality from heart disease (66%) as compared with the incidence (53%) in the general population. New Jersey cardiac physicians are somewhat less obese and follow dietary restrictions more strictly than their noncardiac colleagues. Although stress and strain occur in a vast proportion of all physicians throughout the nation, no statistical evidence supports the popular concept that coronary artery disease is the doctor's disease. Coronary disease occurs more frequently among business executives of the same age group as physicians.

Chronic Granulocytic Leukemia. R. Menéndez Corrada. Bol. Asoc. méd. Puerto Rico 51:354-361 (Oct.) 1959 (In English) [Santurce].

Sixteen men in the early 40's, with chronic granulocytic leukemia, were hospitalized between 1950 and 1958 in the San Patricio Veterans Administration Hospital of San Juan. The diagnosis was made in most of the patients because of the presence of typical symptoms which had lasted for several months. It was also made in a few patients, in complete absence of symptoms, because of the accidental finding of a marked increase in the number of leukocytes and their precursors in the blood. All the patients but 4 had had anemia since the beginning of the disease. Although one of these 4 patients has lived longer than any other patient in the entire group (5½ years), it was found in the other 3 that the presence of anemia at the onset of the disease lacks any prognostic significance. The blood count in the patients on hospitalization was, on an average, 3 million erythrocytes and 170,000 leukocytes per cubic millimeter. The average age of the patients was 43 years. Three patients, who were treated between 1950 and 1953, received irradiation of the spleen as the only treatment, with no satisfactory results. Thirteen patients were treated with busulfan (Myleran), antibiotics, blood transfusion, and bone marrow inoculations between 1954 and 1958. Myleran was well tolerated, but resistance to it proved to be a warning of the occurrence of a blast crisis, which could be prevented by the administration of mercatopurine and large doses of steroids. Large doses of steroids seemed to prevent the crises and to prolong the patient's life.

Eight of the 16 patients died. Death occurred as the result of a blast transformation or crisis in 6 patients, of bronchopneumonia and anemia in one, and from rupture of the spleen in one. The average survival period after start of the treatment was 4 years. Eight patients, all treated with Myleran, are surviving at the present time, at periods which range from 1 to 5½ years since beginning of the treatment. Two patients are living in complete remission, not having had any treatment for 2 and 2½ years respectively. The alkaline phosphatase activity of the granulocytes reappeared during remission in these patients, and reached abnormally high levels which have been maintained up to the present time. Six patients had temporary remissions for periods which ranged from several months to one year; they were followed by relapses which again called for treatment. Myleran is the best available drug in the treatment of chronic granulocytic leukemia; it favors remissions and prolongs the life span of the patient.

The Electrocardiogram of Alcoholic Cardiomyopathy. W. Evans. Brit. Heart J. 21:445-456 (Oct.) 1959 [London].

When the ill-effects of alcohol on the myocardium are slight, withdrawal of alcohol can halt the pathological process, but should the earlier injurious effects go unheaded for some years, the resulting cardiomyopathy will not subside with abstinence from alcohol. It is for this reason that early myocardial damage from alcoholism is so important to detect. The author describes electrocardiographic changes that will facilitate the recognition of alcoholic cardiomyopathy. The first of the 20 patients studied by the author was referred to him by the family doctor on account of breathlessness and with a history of alcoholism over many years. This patient's electrocardiogram presented a change that had not been noticed hitherto in healthy adults or in patients with coronary arterial disease. The remaining 19 patients showed bizarre symptoms and signs associated with characteristic electrocardiographic changes and before a history of alcoholism was obtained. Abnormalities in the electrocardiogram were considered to be distinctive in 17, and although not so specific in the remaining 3, they suggested the diagnosis in these patients also.

The distinctive electrocardiographic deformities were limited to the T wave, which was a depressed dimple in 8 patients, upright and divided in 7, and spinous in 2. Whenever the T wave in chest leads was obviously inverted, as happened in 2 patients, the narrowness of the wave remained as a characteristic feature, and differed from the changes usually met in cardiac infarction. In 3 patients the presence of extrasystoles suggested the diagnosis, because they were multiple, arose from different foci, or were associated with moderate tachycardia. Extrasystoles were also present in company with the distinctive signs in 6 other patients. Auricular fibrillation was found in 2 patients, and paroxysmal auricular tachycardia in another 2. Bundle-branch block, present in 2 patients, and depression of the S-T segment, in 2, were regarded as sinister signs, for they occurred in the presence of enlargement of the heart with failure. Two patients exhibiting such cardiographic signs died. With these exceptions, abstinence from alcohol, together with digitalization in the 2 patients with fibrillation, sufficed to return the patients to health, and without the addition of thiamine therapy.

Administration of Fatty Acids and Arteriosclerosis: Use of the Intramuscular Route. R. L. Romero, N. N. D. de Feuillade and others. Semaña méd. 66:549-552 (Oct. 1) 1959 (In Spanish) [Buenos Aires].

Ten patients with arteriosclerosis were given a meal rich in saturated fatty acids, composed of 300 Gm. of potatoes, 100 Gm. of milk, 100 Gm. of butter, and 70 Gm. of bread. Five patients were given a capsule containing 250 mg. of linolic-linolenic ester after the meal. The remaining 5 received an intramuscular injection of the same unsaturated fatty acid mixture (800 mg. of Linacidin). Electrophoresis and determination of lipemia and cholesteremia were performed on all patients at 4-hour and 24-hour intervals. The results of these tests showed no appreciable changes in cholesteremia. The levels of lipemia, alpha and beta lipoproteins, and Antonini's beta-alpha quotient also decreased in all the patients, regardless of the form of administration of the fatty acids.

The authors conclude that the administration of linolic-linolenic ester is effective, both in preventing postprandial lipemia in patients with arteriosclerosis receiving a diet rich in saturated fatty acids and in lowering existing levels. The fact that no difference is observed between the effects of oral and intramuscular administration points to a lack of interference with the absorption of cholesterol. Apparently the unsaturated fatty acids do not influence the synthesis and resynthesis of cholesterol, and the cholesterol level apparently is not related directly to the sclerosing process. The apparent direct relationship is between arteriosclerosis and the alpha and beta lipoprotein levels. The authors believe that neither the changes in lipoprotein levels nor the absolute cholesterol values reflect the real problem in the etiology of arteriosclerosis. They may be atherogenic stimuli. The fundamental factor must lie in the chemical and textural alterations in the arterial wall as a result of continuous stress and spasm.

The Collection and Storage of Viable Human Fetal Hematopoietic Tissue for Intravenous Use. J. W. Ferrebee, H. L. Lochte Jr., H. Swanberg and E. D. Thomas. Blood 14:1173-1179 (Nov.) 1959 [New York].

The intravenous administration of cellular suspensions of homologous bone marrow induces recovery in a number of animal species after exposures to radiation which otherwise would prove lethal in a few days because of marrow failure. In some species, however, late deaths have been known to occur, and are apparently due to an immunological reaction of graft versus host or of host versus graft or perhaps to a failure to regain immunological responsiveness to endemic disease. Studies on immunological tolerance in fetal tissues suggested that the use of fetal hematopoietic tissue, rather than adult marrow, would diminish the incidence of these delayed deaths. Since evidence in mice has substantiated this point of view, the collecting and storing of human fetal hematopoietic tissues seems pertinent.

From the fact that the human fetus is relatively well differentiated by the end of the second trimester, it might be presumed that marrow obtained at term would have little immunological or hematopoietic advantage over adult cadaver marrow. Yet the authors have placed more emphasis on collecting hematopoietic tissue from the liver and spleen of fetuses of a gestation period of 12 to 20 weeks. The tissues were minced and then passed through a series of increasingly fine screens, of porosity 1,360, 630, 307, 201, 140, and 86 μ respectively. The screened minced tissue was resuspended and passed through a screen of 43 μ aperture. The final suspension contained approximately 0.4 billion liver parenchymal cells, 1.0 billion liver hematopoietic cells, and 0.03 billion splenic cells. This suspension was infused slowly over a 45-minute period without a clinical reaction. Postmortem examination of the recipient 9 days later failed to disclose embolic or other untoward results.

Minced and screened fetal liver and spleen were suspended in a series of dilutions of glycerol and human serum, type AB; 10 minutes at room temperature were allowed for equilibration, and then the several aliquots were cooled to —70C (—94 F) in dry ice. After a period of 6 weeks' storage at —70 C, the specimens were thawed, deglycerolized, and incubated with radiocarbon (C^{14}) formate or with tritiated thymidine. Studies of desoxyribose nucleic acid (DNA) synthesis rates with C^{14} formate and radioautograms after incubation with tritiated thymidine revealed that hematopoietic elements concentrated in these tissues at this stage of gestation maintain their viability during these periods of storage. Intravenous infusion of cellular suspensions prepared from stored frozen tissue, or from fresh tissue in this same age group, produced no observed untoward clinical reaction in the 3 patients studied. These preliminary observations demonstrate that hematopoietic tissue (liver and spleen) from fetuses in the 12-to-20-week gestation period has immunological, and possibly hematopoietic, advantages compared with adult or term fetal marrow. It may be able to acquire tolerance to its host, and it may have greater growth potential.

Staphylococcus Bacteremia: I. Clinical Review of 88 Cases from 1940 to 1958. V. Faber. Ugesk. laeger 121:1593-1601 (Oct. 15) 1959 (In Danish) [Copenhagen].

From 1940 to 1958, 48 men and 40 women with bacteremia due to Staphylococcus aureus were treated in Blegdam Hospital, Copenhagen; 51 cases were diagnosed up to 1957, and 37 cases in 1957-1958. There may be few symptoms at the start, or the onset may be explosive. Diagnosis can be made certain only by blood culture. Of the 34 patients with more or less grave complicating infection, 21 died; of the 54 without complicating infection, 20 died. The lungs were affected in 59 cases and the heart in 25 cases; there was cerebral or meningeal disease in 29 cases, osteomyelitis in 21 cases, and shock in 25 cases. For therapeutic success, early treatment with at least 2 antibiotics in high concentration is necessary, and this treatment should be continued for at least 4 to 6 weeks. Frequent blood culture with examination of the resistance pattern is necessary; it will also allow timely discovery of possible superinfection with other bacteria or fungi. Close supervision and control of cardiac, pulmonary, and renal function and possible complicating disorders are important. In manifest or threatening shock, steroid treatment is indicated.

Staphylococcus Bacteremia: II. Frequency, Origin, Portal of Entry and Mortality Studied in 201 Cases in 1957 and 1958. V. Faber, K. Rosendal and O. Jessen. Ugesk. laeger 121:1601-1607 (Oct. 15) 1959 (In Danish) [Copenhagen].

Staphylococcus aureus is the most frequently diagnosed cause of bacteremia. In 1957 and 1958 bacteremia was verified at the State Serum Institute and the Blegdam Hospital, Copenhagen, in 201 patients by cultivation of Staph. aureus from the blood. Of the 222 strains isolated, only 87 belonged to type 80 or the related type 52/52A/80. Application of antibiotics should be limited, since their use involves danger of change in the bacterial flora in the direction of resistant strains. Bacteremia was found in all age groups and was not restricted to patients with severe primary disease. At least half of the cases were characterized as hospital infections, and 50% of these were directly caused by surgical procedures and parenteral infusions. Otherwise, the most common portals of entry were boils and other cutaneous infections and pulmonary infections. The total mortality rate was 41%; the mortality was higher for infections acquired in hospital than for infections acquired elsewhere.

Staphylococcus Bacteremia: III. Some properties in Staphylococcus Aureus Isolated from Bacteremia Cases and Their Relation to Course of Infection. O. Jessen, V. Faber, K. Rosendal and E. R. Eriksen. Ugesk. laeger 121:1607-1614 (Oct. 15) 1959 (In Danish) [Copenhagen].

Two hundred twenty-two strains isolated from 201 patients with bacteremia due to Staphylococcus aureus were examined with respect to phage group, resistance to antibiotics, and formation of alpha lysin, hyaluronidase, and a lipase; in some cases they were compared with strains from impetigo, furunculosis, and normal nasal mucous membrane. Most of the bacteremia cases were due to strains of phage groups I and III. Most of the strains were penicillin-resistant; resistance to tetracycline occurred mainly in phage group III. Hospital strains were especially resistant. Bacteremia strains did not differ from strains of other manifest infections as to production of alpha lysin or hyaluronidase, and these 2 properties could not be correlated with the course of the infections. The mortality in bacteremia with antibiotic-resistant bacteria was 50 to 60% as against 17 to 40% in infections with sensitive strains. The prognosis was less favorable for bacteremia acquired in hospital than for infections which were not hospital-derived. The mortality was higher in bacteremia caused by lipase-negative strains than in corresponding infections with lipase-positive strains.

The Pathogenesis of Leptospiral Jaundice. F. Ramos-Morales, R. S. Díaz-Rivera, A. A. Cintrón-Rivera and others. Ann. Int. Med. 51:861-878 (Nov.) 1959 [Lancaster, Pa.].

There has been a great deal of speculation on the pathogenesis of jaundice in leptospirosis (Weil's disease). It has been attributed most frequently to hemolysis and intrahepatic biliary obstruction. The authors analyzed data obtained from the study of 235 patients with leptospirosis observed in Puerto Rico from 1948 to 1956. The diagnosis was confirmed by one of the following criteria: (1) isolation and identification of the Leptospira organisms from blood, urine, and/or spinal fluid; (2) serologic evidence of infection (complement fixation and/or agglutination-lysis tests) consistent with the clinical findings; and (3) postmortem evidence. Jaundice developed in 120 of the 235 patients. Since 50% of the patients were hospitalized before the 5th day of illness, the authors had ample opportunity to obtain dependable information on the appearance of jaundice. They found no evidence in support of hemolysis as a dominant factor in the genesis of icterus. No relation of cause and effect of anemia and jaundice was evident. Severe bilirubinemia appeared with unaltered red blood cell or hemoglobin values in the well-hydrated patients. Even among the anicteric, anemia may be attributed to blood loss, either internal or external, a negative nitrogen balance, high fever, azotemia (most prominent among the icteric, but rather common among the anicteric), parasitic infestations with chronic blood loss, and, in some instances, frequent phlebotomies for numerous laboratory examinations.

Laboratory evidence of hepatic dysfunction was recorded in both the anicteric and the icteric: abnormal cephalin flocculation, hyperbilirubinemia, urobilinogenuria, abnormal Bromsulphalein test, and impairment in synthesis of the serum proteins and cholesterol esters. The most intense hepatic dysfunction occurred during the second week of illness, as evidenced by the maximal increases in bilirubin and the alterations in cholesterol esterification. The authors emphasize that there were generally increases in the 1-minute and 30-minute fractions of serum bilirubin. A predominant 30-minute hyperbilirubinemia is occasionally observed early in the course of the disease and during convalescence. This phenomenon may be governed by either a decreased hepatic functional capacity or increasing loads of pigment derived from the reabsorption of tissue hemorrhages. It appears that the latter is of secondary importance in the pathogenesis of jaundice in leptospirosis. Transitory biliary tract obstruction, possibly intrahepatic, may be an aggravating factor in a minority of the jaundiced patients. The role of the impaired renal function in the maintenance of hyperbilirubinemia remains a subject for inquiry. Since there is no evidence to suggest that an increased catabolism of iron porphyrins (myoglobin) contributes to the development of jaundice, it is apparent that the most important factor in the pathogenesis of jaundice in leptospirosis is a decreased functional capacity of the liver.

A Critical Analysis of the Use of Salicylazosulfapyridine in Chronic Ulcerative Colitis. C. G. Moertel and J. A. Bargen. Ann. Int. Med. 51:879-889 (Nov.) 1959 [Lancaster, Pa.].

Reports on the use of salicylazosulfapyridine (also known as Azulfidine, Azopyrine, and Salazopyrine) in the treatment of chronic ulcerative colitis came from Stockholm in 1941. Bargen reported favorable results with it in the United States in 1948. The molecular structure of salicylazosulfapyridine is a combination of salicylic acid and sulfapyridine, these 2 substances being linked by a diazo bond. The studies described were made at the Mayo Clinic on patients with chronic ulcerative colitis, who were treated at the clinic for the first time between 1948 and 1952. The patients so treated were divided into 3 groups: (1) those treated with salicylazosulfapyridine (183 patients); (2) those treated with sulfonamides other [illegible] fapyridine (109 patients); and (3) those treated with general measures alone, or supplemented with antibiotics (131 patients). The aim was to compare the response to these different methods of treatment.

Salicylazosulfapyridine proved to be an effective agent in the control of the symptoms of chronic ulcerative colitis. When compared with treatment with other sulfonamide preparations and with general measures alone, treatment with this drug seemed to be superior in respect to both over-all symptomatic response and duration of hospitalization required to produce a favorable response. Undesirable side-effects occurred in about 1 of 6 patients treated, but these were minor and transitory. Serious hematological complications were rare, but blood counts should nevertheless be made periodically during therapy.

Although the initial response to long-term treatment with large doses of corticotropin (ACTH) or steroids would seem to be comparable to the response obtained with salicylazosulfapyridine, a comparison of length of hospitalization required, complications incurred, problem of withdrawal, and rate of recurrence or relapse seems to show that salicylazosulfapyridine has a very definite advantage. While this drug is not the final answer to the treatment of chronic ulcerative colitis, it has proved of considerable value in controlling the symptoms of the disease. Comparison with other commonly employed therapeutic methods indicated that at present it represents, when combined with the basic general and supportive measures, the treatment of choice of chronic ulcerative colitis.

Familial Hodgkin's Disease: Its Significance and Implications. D. V. Razis, H. D. Diamond and L. F. Craver. Ann. Int. Med. **51**:933-971 (Nov.) 1959 [Lancaster, Pa.].

The study group was composed of 1,102 patients with Hodgkin's disease, who had been seen at the Memorial Center for Cancer and Allied Diseases, New York, from 1918 to 1958. Many more patients with Hodgkin's disease have been seen at the center during these years, but either the histopathological diagnosis was unconfirmed or the case history could not be located. The objective of this epidemiologic study of familial Hodgkin's disease was to determine whether its familial concentration was significant or not. Four control groups were studied: a lymphosarcoma group (1,269 patients); a leukemia group (220); a malignant tumor group (748); and a group of patients with benign diseases (688).

From the data obtained, it appears that Hodgkin's disease occurs in families more often than one might expect from chance coincidence. Due to the great differences in the age distribution in this series, it is hard to be precise about the magnitude of the familial effect. The probability that the immediate relatives of a proband with Hodgkin's disease will also develop the disease is 3 times as great as the probability for the immediate relatives of a proband without the disease. Familial concentration in Hodgkin's disease, though statistically significant, is not very high. In this respect, the situation in Hodgkin's disease resembles most of the instances of reported familial human cancer. Hodgkin's disease apparently does not have a simple inheritance; heredity seems to play a relatively minor or indirect role in its etiology. Whether the familial concentration observed in this study is the consequence of heredity or of the greater environmental similarities for members within the family cannot be determined. The evidence, however, points more to environment than to heredity. Similarities in the time of onset of Hodgkin's disease (unrelated to age) in the affected relatives suggest the importance of "infectious agents." No statistically significant differences were found for familial leukemia and lymphosarcoma.

The Association of Multiple Arthritis with Carcinoma. M. S. Pathy. Rheumatism **15**:73-77 (Oct.) 1959 [London].

While the association of hypertrophic osteoarthropathy with chronic infection and malignant tumors, especially carcinoma of the lung, has become well recognized, it is not generally appreciated that polyarthralgia may be a symptom of carcinoma in various sites in the absence of hypertrophic osteoarthropathy. Two of the 4 patients, whose histories are described, presented with an acute multiple arthritis, and in the other 2 arthritis was a prominent feature of the disease. None of the patients had hypertrophic osteoarthropathy or clubbing of the fingers or toes. One of the patients had bronchial carcinoma, 2 had carcinoma of the stomach, and 1 had carcinoma of the pancreas. The cause of the arthritic manifestations is unknown. It is probable that the association of arthralgia with malignant tumors is more common than is generally appreciated. The possibility of a neoplasm should be considered when multiple joint pains with a raised erythrocyte sedimentation rate and pyrexia occur in a person over 40 years of age.

Evaluation of the Effect of Massive Prednisolone Therapy in Acute Leukemia. B. A. Bouroncle, C. A. Doan and B. K. Wiseman. Acta haemat. **22**:201-208 (Oct.) 1959 (In English) [Basel, Switzerland].

The authors report on 30 patients, 24 of whom had acute lymphatic leukemia, 5 had acute monocytic leukemia, and 1 had acute myeloblastic leukemia. There were 23 males and 7 females, 21 of them being between 18 months and 9 years of age, 4 between 14 and 18 years, and 5 between 19 and 40 years. All 30 patients had been treated with conventional therapy previous to treatment with massive doses of prednisolone; however, this conventional therapy had failed in inducing a remission. Prednisolone was then given orally in an average daily dose of from 500 to 1,000 mg. for 9 to 14 days. The average total dose per course of therapy was 9,300 mg. A complete remission, lasting from 3 to 11 months, was obtained in 7 of the 30 patients. Five of these patients had acute lymphatic leukemia, and 2 had acute monocytic leukemia. A partial remission was obtained in 3 additional patients who had been diagnosed as having acute lymphatic leukemia. No serious side-effects were evidenced in the patients treated in this series.

The results seem to indicate that massive corticosteroid therapy is of value in the treatment of selected patients having resistant acute leukemia. However, use of massive prednisolone therapy initially in the routine treatment of the acute leukemias before other available combinations of drugs have been tried is not recommended.

SURGERY

Surgical Treatment of Aortic Stenosis. R. J. Baird and W. G. Bigelow. Canad. M. A. J. 81:795-800 (Nov. 15) 1959 [Toronto].

The authors report on 65 patients with aortic stenosis, who were operated on at the Toronto General Hospital between November, 1953, and February, 1959. Transventricular dilatation was performed on 59 patients, 42 of whom were adults with pure aortic stenosis. Direct-vision repair with the aid of the heart-lung bypass machine was done in 6 patients who were older children or young adults. Special attention is paid to the group of 42 patients, 39 of whom were men, and the mean age was 43 years; 18 (42%) of the 42 had a positive history of rheumatic fever. The first symptoms were usually anginal pain, faintness or syncope, and dyspnea on exertion. The symptoms progressed rapidly in severity, and the rapidly downhill course after their onset made early operation imperative.

The 42 patients were divided into 4 groups on the basis of their symptoms: group 1 consisted of one patient who had no cardiac symptoms whatsoever; group 2 consisted of 15 patients with syncope and/or anginal pain and occasional mild dyspnea on exertion; group 3 consisted of 16 patients with left heart failure; and group 4 consisted of 10 patients with congestive failure. Seven of the 42 patients died in the hospital, i. e., an over-all mortality rate of 16.7%. The patient in group 1 survived, but 1 patient in group 2, 2 patients in group 3, and 4 in group 4 died; the mortality rate thus varied with the stage of the disease from zero to 40%. A follow-up of 6 months to 6 years revealed that 80% of the patients leaving the hospital are alive with moderate or marked improvement. In recent months the indications for repair under direct vision with the aid of the heart-lung bypass machine have been extended. In the lightly calcified valve of the younger adult, a more complete correction can probably be obtained by operation under direct vision with the aid of the heart-lung pump than by a blind dilatation. In the poor-risk or older patient, it is unlikely that it will supplant the blind transventricular procedure.

Primary Intracerebral Hemorrhage: Results of Surgical Treatment in 244 Consecutive Cases. W. McKissock, A. Richardson and L. Walsh. Lancet 2:683-686 (Oct. 31) 1959 [London].

Since neurosurgeons have become more interested in ruptured intracranial aneurysm, many more patients with acute cerebrovascular accidents have found their way to neurosurgical departments. Many patients admitted for "subarachnoid hemorrhage" have been shown to have cerebral hemorrhage, thrombosis, embolism, and other conditions. Of a total of 2,116 patients who had been admitted to a neurosurgical department because subarachnoid hemorrhage had been suspected, 1,183 had arterial aneurysms, 183 had angiomas, 278 had cerebral or cerebellar hemorrhages, and in 472 no lesions were detectable by angiocardiography. The authors report on 244 patients with primary intracerebral hemorrhage. These were partly derived from the 278 patients mentioned above. Excluded from this group were 28 patients with spontaneous intracerebellar hemorrhage (who are the subject of a separate report), also those with trauma, neoplasm, systemic disease, and primary pontine hemorrhage. There remained 179 cases of primary intracerebral hemorrhage presenting as subarachnoid hemorrhage. To these were added 65 cases in which the cerebrospinal fluid was clear or the findings at lumbar puncture doubtful. The diagnosis in all 244 cases was proved at operation or at postmortem examination.

The generally accepted picture of sudden onset with headache and vomiting, followed rapidly by the development of neurological signs and depression of consciousness, was present in less than half of the patients. In 201 of the 244 patients a lumbar puncture was performed; fresh blood was found in 161, no blood was revealed in 39, and in the remaining patient the result was dubious. In the 43 patients not subjected to lumbar puncture, the ventricular fluid was xanthochromic or blood-stained in 18. Thus, in 179 cases the cerebrospinal fluid indicated recent hemorrhage, in 48 it did not, and in 17 there was doubt. Twelve patients died before surgery could be undertaken, and 1 patient did not require an operation. The 231 patients underwent the following operations: ventricular tapping alone was done in 9; ventriculography, in 14; bur-hole exploration and evacuation of hematoma, in 104; bur-hole aspiration of hematoma with subsequent craniotomy, in 73; and craniotomy for evacuation of hematoma, in 31. There were initially 102 survivors among the 208 subjected to definitive surgery (bur-hole aspiration, craniotomy, or both). During the follow-up period, ranging from 1 to 10 years, 31 of the 102 patients died. The over-all mortality was 74%, and the surgical mortality 51%. Of the 63 survivors, 25 are well but 6 are totally disabled. The mortality is influenced by the following factors: (1) the site but not the size of the lesion (capsular hemorrhages carrying the worst prognosis); (2) hypertension, which is unfavorable; and (3) the state of consciousness, the death rate rising as the level of consciousness falls. The urgent use of ancillary methods of diagnosis (angiography and sometimes exploratory bur-holes) is emphasized.

Transthoracic Repair of Esophageal Hiatus Hernia: Evaluation of 200 Consecutive Cases. L. K. Groves, W. V. Martinez and D. B. Effler. J. Thoracic & Cardiovas. Surg. 38:537-552 (Oct.) 1959 [St. Louis].

In considering the advisability of surgical treatment for herniation of the stomach through the esophageal hiatus, it is important to know what risks are entailed, the probable effectiveness of the surgical treatment, and which patients should be advised to undergo surgery. The authors discuss these questions on the basis of observations on 200 consecutive patients who underwent transthoracic repair of esophageal hiatus hernias in the 6-year period from 1951 to 1956 inclusive. The effective repair of a hiatus hernia involves more than mere reduction of the hernia and "snugging-up" of the hiatus around the terminal esophagus. This form of repair involves a high incidence of recurrent herniation. Many factors, such as vomiting and straining in the postanesthetic period, may elevate the intra-abdominal pressure and force the stomach back up through even a very small hiatus. The placing of sutures from the margins of the hiatus into the friable esophageal musculature does not adequately protect against this hazard.

In the method of repair used by the authors, the free peritoneal cavity is entered by circumferentially incising into it immediately above the esophageal hiatus across the peritonized portion of the thoracic stomach. The upper end of the hernial sac, consisting of parietal peritoneum as well as phreno-esophageal ligament, then retracts to form a cuff that nicely defines the esophagogastric junction and holds sutures firmly. A ring of figure-of-eight sutures is placed deeply into this cuff and some of the underlying musculature. These sutures are brought down through the hiatus, and through stab wounds made with a ligature carrier, out to the superior surface of the diaphragm where they are tied to mattress sutures placed about the stab wounds to fix the esophagogastric junction below the hiatus. In the rare patient, in whom peptic esophagitis has resulted in scarring and fixed esophageal shortening to such an extent that the esophagogastric junction cannot be reduced below the esophageal hiatus, no treatment is completely satisfactory. It is the practice of these authors to raise the esophageal hiatus to the esophagogastric junction by incising upward from the normal hiatus toward the dome of the diaphragm, and to transplant the esophagus forward to this new and elevated position. In this fashion, considerable deficit in length can be overcome, particularly if the phrenic nerve is crushed to elevate the diaphragm maximally. It was necessary to transplant the esophageal hiatus in 20 of the 200 patients. In some of the patients who underwent the conventional repair and in a few who required transplantation on account of a short esophagus, a myotomy was performed in the terminal esophagus.

The results in 180 of the 200 patients who could be followed for from 6 months to 6½ years are tabulated. The results were excellent in 97, good in 52, fair in 15, and the treatment failed in 16 patients. The authors believe that operation is mandatory in a small proportion of patients who have complications, including bleeding, peptic ulceration, stricture of the terminal esophagus, or mechanical obstruction. In the large majority of patients, the operation is elective. These patients will obtain excellent operative results if they are carefully selected for surgery. In retrospect, the largest number of preventable operative failures have been classified as being due to a poor choice of operative candidates, including chiefly emotionally unstable patients and those whose gastrointestinal problems are largely functional.

The Surgical Relief of Chronic Myocardial Ischemia. R. Kauntze, D. McGill and R. Brock. Lancet 2:631-634 (Oct. 24) 1959 [London].

The authors report on 10 men, between the ages of 42 and 62 years, with progressive and incapacitating anginal pain due to overwhelming myocardial ischemia, in the absence of cardiac enlargement, cardiac failure, severe hypertension, and generalized arterial disease. The patients underwent a simple procedure of abrading the parietal and visceral pericardium in an attempt to produce a myocardial reaction sufficiently brisk to improve the intercoronary anastomoses. In all the patients the anginal pain was uncontrolled by treatment preceding the surgical intervention. Of the 10 patients, 9 survived the operation. One of the survivors is outstanding in that he works full time and is quite free from anginal pain with ordinary activity; 10 minutes' exercise failed to produce pain 6 months after the operation. The condition of 2 other patients has improved strikingly, while the results may be classed as good in 5 additional patients. Improvement was slight or absent in only one patient. Serial electrocardiograms were of little value in the assessment of myocardial blood supply after the operation, and the assessment of these patients was mainly on clinical evidence. Improvement in pain and dyspnea on effort has been most 4 months after operation, when the psychological effects of special investigation and operation and follow-up would be expected to be waning, if not already absent. Fatigue was a particular complaint in early convalescence, although right ventricular failure occurred in the immediate postoperative period in only one patient; it cleared up within 3 weeks.

Diagnosis of Thyroid Cancer: Forty Cases of Infiltrating Carcinoma. O. F. Grosso, P. Paseyro and J. Maggiolo. An. Fac. med Montevideo 44:53-80 (Jan.-April) 1959 (In Spanish) [Montevideo, Uruguay].

Forty patients with infiltrating carcinoma of the thyroid were observed in the Instituto de Endocrinologia of the Faculty of Medicine of the University of Montevideo. Thirty-four of the patients were female, and 6 were male; they were observed for the first time at an age which ranged between 11 and 75 years. Carcinoma of the differentiated type was found in 35 patients, and of the undifferentiated type in 5. The group of patients with differentiated carcinoma included 20 with papillary carcinoma and 12 with follicular adenocarcinoma; one patient had a Hürthle-cell tumor, and two had a solid thyroid tumor. The greatest incidence of differentiated carcinoma was in patients between 41 and 50 years of age; undifferentiated carcinoma occurred mostly in patients between 55 and 65 years of age.

Diagnosis of differentiated thyroid carcinoma is difficult. The following clues are suggestive: (1) presence of a nodular goiter, especially in children and in young adults; (2) a thyroid tumor of rapid growth; (3) simultaneous or successive appearance of a thyroid tumor and of cervical lymph node enlargement; (4) recurrence of a thyroid tumor after resection; and (5) signs, symptoms, or presence of visceral, bone, or lymph node metastases of unknown origin. Puncture cytology is of value in deciding the diagnosis of undifferentiated thyroid carcinoma.

Lobectomy for Bronchial Carcinoma. J. R. Belcher. Lancet 2:639-642 (Oct. 24) 1959 [London].

The author reports on 264 patients with bronchial carcinoma, who underwent lobectomy and were followed up for 5 years or more. Of the 264 patients, 12 died as a direct result of the operation, and an additional 6 were lost to follow-up. Of the remaining 246 patients, 141 died less than 5 years after the operation, 14 died between 5 and 10 years after the operation, and 91 (37%) were alive at 5 years. Thirty (12%) of the 246 patients died of causes other than bronchial carcinoma, and, if these are excluded, the 5-year survival rate is 42%. The 5-year survival rate among patients with adenocarcinoma was 53%; among those with oat-cell carcinoma, 37%; and among those with squamous carcinoma, 32%. This difference was not due to the different incidence of invasion of lymph nodes. The 5-year survival rate among patients with involvement of lymph nodes was 23%, as compared with 43% among those in whom the lymph nodes were tumor-free. The survival rate was significantly better among patients with lower-lobe tumors (44%) than among those with upper-lobe tumors (31%). Carcinoma developed in the residual lung of 19 patients (7.5%); in 11 patients it was thought possible that these might be new primary tumors.

If lobectomy, as compared with pneumonectomy, were an inadequate operation, the tendency toward conservatism in the surgical treatment of bronchial carcinoma would have been reflected in a lower over-all survival rate. This has not been shown. It seems, therefore, that on both pathological and statistical grounds the present popularity of the more conservative resection in the treatment of bronchial carcinoma is justified.

Ventricular Aneurysm Following Myocardial Infarction: Results of Surgical Treatment. D. A. Cooley, W. S. Henly, K. H. Amad and D. W. Chapman. Ann. Surg. 150:595-612 (Oct.) 1959 [Philadelphia].

Ventricular aneurysm is a frequent late complication of extensive myocardial infarction. Although cardiac rupture is rare, serious and frequently incapacitating symptoms result from the impairment of cardiac function produced by the noncontractile, expansile aneurysm. Embolism from mural thrombi may also produce serious complications. The authors present observations on 6 patients in whom aneurysm of the left ventricle resulted from myocardial infarction. In all of them excision of the ventricular aneurysm was performed with the aid of a pump oxygenator for temporary cardiopulmonary bypass. A stainless steel oxygenator based upon the bubble diffusion principle was used. DeBakey roller pumps of the complete occlusion type were used to withdraw venous blood from the venae cavae and to return oxygenated blood to the systemic arterial system. Cardiac catheterization studies were performed prior to surgery in 5 of the 6 patients. They revealed a reduction in cardiac output and significant pulmonary hypertension. After operation cardiac function improved, and all patients obtained clinical benefit. The pathological state of the diseased myocardium determines the optimum time for the surgical intervention after myocardial infarction.

Another complication of severe myocardial infarction, which the authors treated by open cardiac techniques, was acute perforation of the interventricular septum. The histories of 2 patients with this complication are briefly described, because they support the opinion that after infarction a delay of at least 6 weeks, and preferably 3 months, is necessary for satisfactory ventricular recovery. Surgical excision and ventricular repair are a feasible and rational surgical treatment for ventricular aneurysm after myocardial infarction when the lesion is of sufficient size to cause impairment of cardiac function.

Continuous Endobronchial-Pulmonary Medication: Preliminary Note. L. Bonelli, L. Baglione, D. Rochat and G. Bologna. Minerva med. 50:3275-3290 (Oct. 17) 1959 (In Italian) [Turin, Italy].

Continuous endobronchial-pulmonary treatment with perfusion, with drugs introduced through a plastic tube into the respiratory system by the cricothyroid route, was given to 97 patients. Good results were obtained in 8 patients with bronchiectasis, in the sense that peribronchial disorder disappeared and discharge was reduced or eliminated. Of 4 patients with pulmonary abscess, complete remission was obtained in 1 patient who had the acute phase of the disease, and good or very good results in 3 patients who had the chronic variety of the disease. Eighty-five patients with chronic tuberculous cavities, who had been hospitalized for more than a year, received the treatment for the purpose of ameliorating severe localized conditions. Improvement was obtained in 52 patients, but there was no change in 28 patients, and deterioration in 5. The patients tolerated the insertion of the plastic tube well, and almost all became accustomed to carrying it after a few days. A subcutaneous cervicofacial emphysema developed in 2 patients, who had avoided bed rest during the first day of treatment; the condition was resolved in 2 days. The tube, which broke internally in 4 patients, was removed by bronchoscopy; the break was probably related to faulty material. The authors conclude that the experience with this procedure warrants its further application. They suggest inserting the tube in some of the patients 30 days before and resuming its insertion after the pulmonary resection.

Pericarditis Following Pneumonectomy for Pulmonary Tuberculosis. P. De Roover and A. Lacquet. Brit. J. Dis. Chest 53:356-359 (Oct.) 1959 [London].

A case of exudative pericarditis occurring after pneumonectomy for pulmonary tuberculosis is reported. The patient, a 46-year-old man, had had pulmonary tuberculosis for over a year. His right upper lobe was shrunken and contained many cavities. The patient was admitted to the tuberculosis department of the University Clinics in Louvain, Belgium, where he was treated with tuberculostatic agents and complete rest. After a 7-month treatment the sputum became negative, and a pneumonectomy was performed, with removal of part of the pleura. The lower lobe could be freed without opening the pericardium. The immediate postoperative course was fairly good. On the 16th postoperative day the patient suddenly developed fever and became dyspneic; ascites and edema developed progressively in the lower limbs; the blood pressure dropped, and the circulation rate became markedly slow. A roentgenogram showed hydropneumothorax on the right side, while the only abnormal electrocardiographic finding was a flattened T wave. A few days later, as the roentgenologic examination revealed a markedly enlarged heart shadow, a puncture of the pericardium was performed, with drainage of 400 cc. of a seropurulent fluid. The patient improved immediately, and the blood pressure rose from 55/45 to 110/70. The puncture was repeated later, but the patient declined rapidly and died one month after the operation.

The authors call attention to the danger of an unnoticed exudative pericarditis which may be concealed behind the diagnosis of "cardiac decompensation." Before establishing such a diagnosis, the possibility of an exudative pericarditis should be investigated. Pericarditis should be suspected whenever the patient has a prolonged period of fever after the operation. The prognosis is poor, although pericardial punctures may bring about a complete cure.

The Operative Risk in Cardiopathic Women. G. Atlante and G. Giorgetti. Policlinico (sez. chir.) 66:350-374 (Oct.) 1959 (In Italian) [Rome].

The authors report a study on a series of 419 cardiopathic women, 24 to 79 years of age, operated on for gynecologic diseases at the gynecology and obstetrics clinic of the University of Rome from January, 1953, to December, 1957. One hundred seven patients were suffering from mitral insufficiency, 23 from mitral insufficiency and stenosis, 19 from aortic lesion, and 6 from mitral and aortic lesions. One hundred eighty-seven patients were operated on for fibromatosis of the uterus, 51 for cancer of the endometrium, and 40 for cancer of the neck of the uterus. Laparotomy was performed on 345 patients (82.3%), vaginotomy on 70, vesicotomy on 2, and mastectomy on 2. Good results were obtained in most instances. Among the survivors were 6 patients with atrial fibrillation, 2 of whom underwent total hysterectomy; 1, subtotal hysterectomy; 1, vaginal hysterectomy with plastic;

1, myomectomy; and 1, explorative laparotomy. Each of these patients received digitalis during and after the operation; anesthesia was induced with thiopental (Pentothal) and a mixture of nitrogen peroxide and oxygen. Results were also good in 207 patients whose electrocardiograms showed signs of damage to, alterations or lesions of the myocardium, and an abnormal rhythm. Only 3 postoperative incidents of paroxysmal tachycardia were recorded.

Anesthesia was induced by means of Pentothal, tubocurarine or succinylcholine, nitrogen peroxide and oxygen in 388 instances; by Pentothal and oxygen in 12; by ether and Pentothal in 4; by ether, nitrogen peroxide, and Pentothal in 5; by ether only in 7; and by spinal anesthesia in 1. Nitrogen peroxide was administered as a local anesthetic to 2 patients. Cardiovascular disturbance followed the operation in 16.8% of the cases. Ten of the 419 patients died. In 3 patients, however, death was the result of causes not related to the cardiopathy; 2 of these patients died of neoplastic cachexia and liver insufficiency due to metastases of carcinoma of the ovary, and 1 of severe septicemia. None of the patients died during the operation, and one died the first day after the operation.

The authors believe that, though the operative risk has been greatly reduced in cardiopathic patients, it is still useful to consider each case individually and to adopt an attitude of "preventive diffidence." On the basis of this the most suitable preoperative therapy and the least traumatic operation, as well as the most suitable anesthetic and postoperative treatment, will be chosen.

Spontaneous Idiopathic Segmental Infarction of the Omentum. H. N. Blansfield and P. C. Jameson. Connecticut Med. 23:697-699 (Nov.) 1959 [New Haven].

The authors report 2 patients with spontaneous idiopathic segmental infarction of the omentum. The first patient, a 6-year-old girl, was admitted to Danbury (Conn.) Hospital with severe abdominal pain of 2 days' duration, localized in the right lower quadrant, accompanied by anorexia and vomiting. Her history revealed a mild infection of the upper respiratory tract, associated with coughing, one week before admission. There was no history of constipation, of diarrhea, or of trauma. Physical examination was unremarkable except for tenderness in the right lower quadrant of the abdomen, with spasm and rebound tenderness. A diagnosis of acute appendicitis was made. At laparotomy a serosanguineous fluid was encountered in the abdominal cavity. The appendix was normal, but a firm rubbery mass of omentum covered with fibrinous exudate was found in the right upper quadrant. This lesion was resected, and appendectomy was performed. Pathological examination of the surgical specimen revealed congestion, hemorrhage, and perivascular infiltration with polymorphonuclear leukocytes. The vessels were thrombosed. The pathological diagnosis of omental infarction was made. The patient's postoperative course was uneventful.

The second patient, a 72-year-old woman, was admitted to Danbury Hospital because of pain in the right lower quadrant of the abdomen for the last 5 days, which was aggravated by walking and standing. She had no nausea and no vomiting. The patient's history revealed that 3 weeks before admission she had had a mild infection of the upper respiratory tract, associated with laryngitis, bronchitis, and mild coughing, and that 12 years before she was subjected to hysterectomy and appendectomy. Roentgenograms of the gastrointestinal tract were normal. Physical examination of the abdomen revealed a palpable lemon-sized tender mass in the right iliac fossa. There was no rebound tenderness and no rigidity, but voluntary spasm was present on deep palpation in the right lower quadrant. A diagnosis of a retroperitoneal tumor was made, with the possibility of a lymphosarcoma. At laparotomy a lemon-sized infarcted mass of omentum was found adherent to the anterior cecal wall. The infarcted tissue occupied the right free border of the omentum. The intestine revealed no intrinsic disease, such as tumor, ulceration, or diverticulitis. There was no torsion of the omentum, and no adhesions surrounded it. The infarcted omental mass was resected. The pathological diagnosis of omental infarction due to unknown cause was made. The patient's postoperative course was uneventful.

It is of interest to note that both patients had had infection of the upper respiratory tract before onset of the abdominal symptoms. This corresponds with Totten's theory that increased abdominal tension, coincident with coughing and sneezing, might be sufficient to cause rupture of the omental veins, leading to hemorrhage and secondary thrombosis. Omental infarction is a significant cause of error in the diagnosis of abdominal disease. This lesion should be considered in patients manifesting vague, atypical abdominal symptoms, in both acute and chronic conditions.

Frequency of Staphylococci Resistant to Penicillin and Streptomycin in Infections in Surgical Out-Patients. K. R. Eriksen and N. Dons. Ugesk. laeger 121:1553-1556 (Oct. 8) 1959 (In Danish) [Copenhagen].

Staphylococcus aureus was isolated from 1,136 outpatients with abscesses, boils, paronychia, and other subcutaneous infections. From 1949 to 1958 the frequency of penicillin-resistant staphylococci rose from 10 to 57.6% and the frequency of streptomycin-resistant staphylococci, from 0 to 35.5%. In the 814 patients who had not had contact with hospitals and had not been treated with antibiotics, the frequency of penicillin-resistant staphylococci rose from 4.5 to 46.1% and the frequency of streptomycin-resistant staphylococci, from 0 to 22.6%.

Hypoglycemia Due to Nonpancreatic Mesodermal Tumors: Report of Two Cases. D. R. Miller, R. E. Bolinger, D. Janigan and others. Ann. Surg. **150:** 684-696 (Oct.) 1959 [Philadelphia].

Although Whipple's triad, consisting of "attacks of nervous or gastrointestinal disturbances in the fasting state, associated with hypoglycemia and immediate relief of symptoms after the ingestion of glucose," may be produced by intrinsic liver disease, adrenal insufficiency, or pituitary disturbances, the surgeon's primary interest in the triad has been its association with functioning islet-cell tumors of the pancreas. There have also been reports on nonpancreatic tumors associated with Whipple's triad. The authors were able to trace literature reports on 15 such patients, and they present the histories of 2 additional patients who were studied at the University of Kansas Medical Center, Kansas City. One patient was a 73-year-old man, and the other a 59-year-old woman. The clinical features observed in these 2 patients were like those found in 15 previously reported patients.

Distal pancreatectomy did not abolish the hypoglycemia in either of these patients. In the first patient, removal of a large pelvic tumor was not possible, and he died as the result of complications of the large pelvic sarcomatous mesodermal tumor involving the prostatic area. The second patient completely recovered after removal of a large diaphragmatic fibrous mesothelioma. Assays for insulin activity were done upon tumor tissue from both patients. Postmortem autolysis probably prevented finding insulin activity in the tumor of the first patient. In the second patient, insulin activity was demonstrated, lending support to the theory that an insulin-like substance is produced by the tumor. The characteristics of the tumors and theories of hypoglycemia etiology are discussed.

The Physiological Response of the Small Bowel of the Dog to Ischemia Including Prolonged in Vitro Preservation of the Bowel with Successful Replacement and Survival. R. C. Lillehei, B. Goott and F. A. Miller. Ann. Surg. 150:543-560 (Oct.) 1959 [Philadelphia].

New surgical techniques and ideas for treating conditions involving the intestine and/or its vasculature have been slow to evolve, because of misgivings that anastomoses involving these vessels will not remain open. There is insufficient knowledge about the ability of the small intestine to survive complete or partial occlusion of its vasculature while conditions affecting the superior mesenteric vessels are dealt with. Finally, nothing is known about the fate of the small intestine after severance of its connections with the central nervous system and after division of its lymphatic drainage. In studies on the effect of ischemia on the small intestine of dogs, the authors made serial determinations of the plasma volume, hematocrit, and plasma hemoglobin before, during, and after experiments, as well as gross and microscopic observations on the intestine itself.

It was found that the majority of adult mongrel dogs tolerated up to 3.5 hours of superior mesenteric arterial occlusion if the collateral circulation to the small intestine was not disturbed. If all collateral circulation to the intestine was occluded as well, then most dogs died after a 3-to-3.5-hour occlusion of the superior mesenteric artery. Interruption of all circulation to the small intestine for 2 hours was tolerated if the intestine was allowed to cool to room temperature, 25 to 28 C (77 to 82.2 F). If, however, the intestine was cooled to 5 C (41 F), then it was safe to interrupt all circulation to the small intestine for at least 5 hours.

Knowing this, the authors removed the entire small intestine, save for the first few centimeters of duodenum, and held it in vitro. No external cooling of the intestine was required if it was returned to the peritoneal cavity and circulation reestablished within 2 hours. If cooled to 5 C (41 F) in vitro, it was not necessary to reestablish circulation for up to 5 hours. In every case the intestine retained its viability, and many of the dogs survived for weeks or months, indicating that the intestine could survive complete severance of all connections with the central nervous and lymphatic systems and that anastomoses of the superior mesenteric vessels, especially those of the veins, would remain open. This technique was also used to make small intestine homografts in dogs, which have so far lasted up to 7 days.

Hodgkin's Disease of the Cecum: Report of a Case. W. A. D. Alonzo. J. Internat. Coll. Surgeons 32:479-490 (Nov.) 1959 [Chicago].

The author reports a case of Hodgkin's disease in a 23-year-old man in whom the disease was first manifested in the cecum and clinically resembled appendicitis. On admission to St. Joseph's Hospital in Philadelphia, the patient had severe continuous pain in the right lower abdominal quadrant, with no radiation. He felt nauseated after having eaten breakfast. Marked tenderness and some muscle guarding were elicited over McBurney's point. Rectal examination elicited a great deal of tenderness in the right side of the pelvis, but no masses were detected by palpation. The temperature was 99 F (37.2 C). The hemoglobin level was 12.3 Gm. per 100 cc., the erythrocyte count was 4 million per cubic millimeter, and the leukocyte count was 10,300 per cubic millimeter. A diagnosis of appendicitis was made, and the patient was operated on. The appendix was normal, but the cecum contained a hard, firmly fixed mass, posteriorly situated and about the size of an orange, which was thought to be a carcinoma. The serosa was edematous and injected. The incision was closed in layers, and the patient was prepared for right-sided colectomy with succinylsulfathiazole (Sulfasuxidine), given for 3 days, and neomycin, given for 24 hours. On reoperation, normal conditions were observed throughout, except for the hard fixed mass in the head of the cecum. Just below and medial to the cecal mass were 2 firm and discrete lymph nodes, each about the size of an almond. The terminal portion of the ileum, cecum, and ascending colon to the midtransverse portion were resected, and an end-to-side ileotransverse colostomy was performed. Gross and microscopic examination of the operative specimen revealed Hodgkin's disease, involving the cecum and 2 out of 7 regional lymph nodes. The resected margins were free of disease. The patient was carefully studied for systemic evidence of the disease, with negative results. He made a good recovery from the operation, returned to work as an automobile mechanic, and offers no complaints.

Hodgkin's disease may occur in the gastrointestinal tract, though its primary occurrence in the cecum is rare and may be confused grossly at the operating table with carcinoma. The author reviewed the literature on Hodgkin's disease of the gastrointestinal tract in general, with special emphasis on the cecum. Hodgkin's disease of the cecum occurs chiefly in the third decade of life. Its incidence is the same in men as in women. The clinical picture is characterized by dull, constant pain in the right lower quadrant of the abdomen, associated with anorexia, nausea, and slight loss of weight. Neither hematemesis nor melena was usual or frequent in the cases collected from the literature. Some of the workers advocated surgical resection combined with roentgenotherapy for localized Hodgkin's disease of the gastrointestinal tract. When the lesions are inoperable or surgical intervention is contraindicated, roentgenotherapy is advocated for the amelioration of symptoms and the prolongation of life. The opinion has been expressed that in cases of Hodgkin's disease localized to the cecum, in which resection has been done, roentgenotherapy should not be used.

Hydrocortisone in Surgical Stress. E. M. Greisheimer. J. Am. M. Women's A. 14:897-899 (Oct.) 1959 [Baltimore].

The author mentions 3 important groups of hormones that are elaborated by the adrenal cortex. She is concerned with hydrocortisone, the chief constituent of the corticoid group of hormones, which during and after periods of stress, such as in connection with surgical operations, may be found in increased quantities in the peripheral blood. If one is to treat chronic adrenal insufficiency or acute adrenal insufficiency arising during or immediately after surgery, one should know the amount of hydrocortisone produced by the adrenal glands in normal individuals. It has been estimated by radioactive methods that the human adrenal glands supply about 30 mg. of hydrocortisone or similar steroid daily. A person who has undergone total adrenalectomy needs about 1 mg. of hydrocortisone, given by intravenous infusion hourly, to remain free of symptoms of adrenal insufficiency.

After satisfactory methods of determining hydrocortisone levels in the plasma became available, a test of adrenocortical capacity was devised, based on changes in plasma levels of hydrocortisone during and after administration of corticotropin (ACTH). Fifteen to 25 I. U. of ACTH in saline or dextrose solution are given intravenously over a period of 4 to 6 hours. The level in plasma rises markedly in the presence of normal adrenal glands and returns to the initial level about 6 hours after the cessation of infusion. The response is decreased in Addison's disease, entirely lacking in the absence of adrenocortical tissue, and exaggerated in patients with adrenal cortical hyperfunction (Cushing's syndrome) and in normal women during the third trimester of pregnancy. There is increased activity of the adrenal cortex, probably due to emotional stress, during the preoperative period. Since it is possible to evaluate the capacity of a patient's adrenal cortex before surgery and, in view of the information about the daily amount of hydrocortisone produced, it is advisable to administer this hormone in adequate doses to patients whose adrenal glands are unable to respond normally to the stress of surgery. Hydrocortisone therapy offers a means of protecting patients from postoperative shock. Serious postoperative complications may ensue if the adrenal glands are hypoactive and hydrocortisone therapy is neglected. Histories of surgical patients should always include information regarding previous use of cortisone, hydrocortisone, or ACTH therapy, because if a patient has been taking cortisone or hydrocortisone, surgery may produce an adrenal crisis.

Changes in Number of Thrombocytes Under the Influence of Brain Surgery. W. Umbach, E. Grözinger and K. Hummel. Klin. Wchnschr. 37:1069-1073 (Oct. 15) 1959 (In German) [Berlin].

Every surgical trauma causes changes in the blood distribution and in this way brings about alterations in the thrombocyte count in the circulating blood. In interventions on the central nervous system, the centers that regulate the composition of blood are influenced, and thus there occur, in addition to the "traumatically" elicited thrombocyte fluctuations (loss by hemorrhage or by the formation of coagulation thrombi), changes in the regulatory mechanisms for thrombocytopoiesis and thrombokinesis. Continuing earlier studies, the authors investigated the number of thrombocytes, before, during, and after surgical interventions, in the brains of 53 patients. The operations included 18 on the cerebrum and 8 on the cerebellum; there were 7 ventriculographies (which in 6 cases were immediately followed by cerebellar interventions), 4 stereotactic exclusions in the regions of the subcortical nuclei for parkinsonism, and 9 spinal operations; the others included exclusions of the hypophysis with radiogold (Au^{198}) or irradiations of localized tumors by radio cobalt (Co^{60}).

In the course of most of these operations, the number of thrombocytes decreased during and in the first 24 hours after the operation. This initial decrease results from the surgical blood loss, but particularly from the physiological "consumption" of the thrombocytes during hemostasis. Very great, and sometimes prolonged, fluctuations in the number of thrombocytes occurred during interventions on the hypophysis, in the course of ventriculographies, in the presence of hydrocephalus, and in deep-lying processes close to the diencephalon. Increases in thrombocytes predominated; the initial thrombocyte count was often exceeded, and this increase frequently persisted for a relatively long period. This is probably caused by an irritation of the hematopoietic centers in the diencephalic regions, which alter the emergence of the thrombocytes from the bone marrow and their distribution in the blood stream. There is a parallelism between these changes in the thrombopoietic system and the known changes in the leukopoietic and erythropoietic systems after central nervous system irritations. These findings complement earlier information about the central regulation of the hematopoiesis.

Physiologic and Surgical Problems in the Management of Primary Aldosteronism. B. Zimmermann, W. H. Moran Jr., J. C. Rosenberg and others. Ann. Surg. 150:653-665 (Oct.) 1959 [Philadelphia].

Patients with primary aldosteronism present themselves usually with a history of hypertension of considerable duration, in addition to which they commonly complain either of muscular weakness or of paralysis of an intermittent or recurrent nature. In association with metabolic alkalosis, the carpal and pedal spasm of tetany is frequently seen, and Trousseau and Chvostek signs may be elicited. Other interesting findings are polyuria and polydipsia, phenomena which are in consonance with earlier observations that chronic administration of mineralocorticoids results in a "diabetes-insipidus-like" picture. The usual aldosteronism complex does not include edema, but excessive aldosteronism has been found associated with edema. The authors present observations on 5 patients with aldosteronism, 4 of whom were operated on. In the 5th patient the diagnosis of aldosteronism seemed proved by the fact that the excretion of aldosterone was about 10 times the normal range. Two of the patients had benign tumors, 1 had carcinoma, and 1 had hyperfunction without tumor. Aldosterone excretion ranged from 8 mcg. per 24 hours in one patient with adrenal adenoma to 180 in the presence of a metastasizing adrenal carcinoma.

In 2 patients the administration of corticotropin (ACTH) caused a striking increase in aldosterone excretion. This observation seemed to refute the idea that the response to ACTH might be used to differentiate hyperplasia from tumor, because a 10-fold increase was produced by ACTH in a patient with a highly malignant tumor. In 2 of 3 patients the addition of potassium to the diet caused an increase in aldosterone output. This may be of diagnostic value in patients in whom the basal value is in the borderline range. Although aldosterone may be mobilized by potassium administration, it is possible to produce positive potassium balance in these patients with rapid reversal of alkalosis, hypopotassemia, and electrocardiographic changes. Failure to restore potassium balance before operation involves an unnecessary surgical hazard. Furthermore, because of the synergistic effect of potassium deficiency and curare-like compounds, curare preparations should not be used in the anesthesia of patients with aldosteronism.

A transabdominal approach is suggested for exploration, because aldosterone-producing tumors may be very small, and the contralateral atrophy which is seen in pituitary basophilism (Cushing's disease) is absent. Diagnostic problems may arise from the fact that other mechanisms can cause hypopotassemic alkalosis. Two of the cases presented illustrate the occasional effects of chlorothiazide and of chronic abuse of cathartics in the genesis of clinical potassium depletion. The determination of urine pH and salivary sodium/potassium ratio have not been helpful. Such cases emphasize the necessity for specific aldosterone determinations.

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Progressive Muscular Dystrophy: Genetic Relation with Creatinine Metabolism. D. Brage and I. Noviski. Rev. Asoc. méd. argent. 73:333-336 (Sept.) 1959 (In Spanish) [Buenos Aires].

Two brothers, 16 and 14 years old, were observed in the Hospital Alvear of Buenos Aires. The patients had been normal up to the age of 7 years, after which they started to complain about numbness, pain, and marked weakness of the legs and the arms. The patients became unable to walk and to use the arms at the age of 11 years. The symptoms were typical of progressive muscular dystrophy of the Leyden-Moebius type. Only the muscles of the face and neck and certain muscles of the thorax were spared. No causal spinal lesion was found by neurological examination as causal factor of the disease. The metabolism of creatinine was unbalanced in both patients. It was normal in all members of the family (parents, grandparents, brother, and sister). A sister of the mother had suffered with the same muscular disease; she died at the age of 24 years. The authors conclude that progressive muscular dystrophy of the Leyden-Moebius type is a recessive hereditary disease due to a familial inbalance of the metabolism of creatinine.

A Method of Treatment for Delirium Tremens. R. Cantoni and M. Burner. Schweiz. med. Wchnschr. 89:1111-1113 (Oct. 17) 1959 (In French) [Basel, Switzerland].

The authors report on 30 patients, between the ages of 33 and 61 years, with delirium tremens, who were admitted to the psychiatric clinic of the University in Lausanne, Switzerland, in 1958 and were treated by a standardized method. They were given a slow intravenous injection of a mixture of 40% solution of fructose, strophantin, acetylmethionine, and vitamin C, followed immediately by an intramuscular injection of hepatic extracts. At intervals of 8 and 16 hours the patients were given again an intravenous injection of 40% solution of fructose. This treatment had been instituted for a 24-hour period and was repeated daily for the duration of the psychotic attack and for 24 hours after its termination. During the full length of the attack the daily fluid intake of the patients was limited to 1,500 to 2,000 cc., with the exception of extremely dehydrated patients. In certain cases, when it appeared necessary to employ sedatives, the patients were given promethazine in small doses. The use of opiates, tranquilizers, and barbiturates was entirely abandoned because of the dangers associated with the administration of these drugs during attacks of delirium tremens. All forms of restraint were omitted. The authors attempted to utilize the suggestibility of the alcoholic patients. A certain calmative effect, followed occasionally by sleep, was frequently obtained by suggestions aimed at inducing a hypnotic sleep. The results obtained with this therapeutic method were equal, and sometimes even superior, to those obtained by other methods of treatment, which are undoubtedly effective but are not always as harmless. Agitation, oneirism, and tremor were attenuated progressively and made way for a recuperative sleep. The average duration of the psychotic attack was 41 hours, the shortest period being 14 hours and the longest 75 hours.

Polyradiculitis. T. O. Iversen. Ugesk. laeger 121: 1562-1567 (Oct. 8) 1959 (In Danish) [Copenhagen].

The etiology and pathogenesis of polyradiculitis are unknown. Pathologically, a variable, but often considerable, number of nerve roots are the seat of infection or toxic degenerative changes, and not infrequently the whole axon is involved in the pathological process. Polyradiculitis may occur in combination with infectious diseases, especially mononucleosis. The symptoms depend on which and how many nerve roots are affected. The temperature is usually normal, both at the onset and during the course. Albuminocytological dissociation is the rule. Apart from the cases with respiratory paresis, the prognosis is usually good. Antibiotic treatment is thought to be without effect in the acute stage. In the Odense District and City Hospital, 17 patients (10 males and 7 females, 6 aged 15 years or less) with acute polyradiculitis were admitted during the last 4 years, most of them within 4 weeks after the onset of the symptoms. In 5 patients the symptoms set in with fever, but the temperature became normal within a few days. In 8 patients the sedimentation rate was elevated, varying from 15 to 87 mm. Changes in the spinal fluid were seen in 16 patients on the first puncture, and in 1 patient on repuncture a week later. Only 12 patients had primary albuminocytological dissociation on the first lumbar puncture; in the others there were varying changes with both increased albumin and cell count. There was no correlation between the clinical course and the changes in the spinal fluid. In 3 patients changes in the spinal fluid persisted in spite of marked improvement in the clinical condition, and 4 showed no signs of clinical improvement although the spinal fluid had become normal. On discharge, the condition of 13 patients was distinctly improved, in 3 the clinical condition remained unchanged, and 1 patient was transferred for further respirator treatment because of exacerbation with alarming respiratory paralysis.

GYNECOLOGY & OBSTETRICS

Vaginal Trichomoniasis: Influence of Pregnancy and of the Menstrual Cycle on the Incidence of T. Vaginalis Donné, 1837. M. P. Barreto, P. V. Oliveira, H. Zago Filho and others. Rev. Assoc. méd. brasil. 5:220-227 (Aug.) 1959 (In Portuguese) [São Paulo, Brazil].

In a previous paper, an abstract of which appeared in The Journal (171:2018 [Dec. 5] 1959), the authors reported on the role of Trichomonas vaginalis and of Candida species in the etiology of leukorrhea, as observed in a series of 593 women who had received a detailed gynecologic examination at the Mercy Hospital in Ribeirão Preto, Brazil.

In this article the authors report on the same group of patients in relation to the incidence of T. vaginalis as influenced by pregnancy and by the menstrual cycle. A series of 514 women were selected from the total number examined, and subdivided into 2 groups, one composed of 256 pregnant women, and the other of 258 nonpregnant, normally menstruating women. Investigations of T. vaginalis and of Döderlein's bacilli, as well as determination of the vaginal pH, were performed on all the patients. Infection with T. vaginalis was found in 40.7% of the nonpregnant women and in 39.8% of the pregnant.

T. vaginalis was present in 43% of the women in the first trimester of pregnancy, in 37.8% of those in the second, and in 35.5% of those in the third trimester. In the nonpregnant women, the incidence of infection with T. vaginalis was high (47.7%) during the menstrual phase; it increased (51%) in the immediate postmenstrual interval and dropped to a minimum (17.4%) in the postovulatory period. The average pH values showed parallel fluctuations, while the incidence of Döderlein's bacilli showed the opposite trend. The authors conclude that the variations in incidence of T. vaginalis, as correlated with the various phases of pregnancy and of the menstrual cycle, explain, at least in part, the discrepancies found in medical statistics regarding the frequency of trichomoniasis.

Folic-Acid Deficiency in Pregnancy: The Pathogenesis of Megaloblastic Anemia of Pregnancy. I. Chanarin, B. M. MacGibbon, W. J. O'Sullivan and D. L. Mollin. Lancet 2:634-639 (Oct. 24) 1959 [London].

The authors performed folic-acid clearance tests by following the rate of clearance from the plasma of a small dose of folic acid given intravenously to 241 pregnant women without anemia, to 11 pregnant women with untreated megaloblastic anemia, and to 30 healthy women who served as controls. The absorption of folic acid was studied by following the rise in the serum folic-acid level, after the oral administration of a small dose of the vitamin, in 90 healthy persons of both sexes, in 45 women who were between 20 and 40 weeks pregnant, and in 10 pregnant women with treated megaloblastic anemia. The rate of clearance of folic acid from the plasma was increased in 66% of the pregnant women in late pregnancy and in all the patients with twin pregnancy. These findings justify the conclusion that the increased rate of clearance is due to folic-acid deficiency. This deficiency appears likely to be due mainly to the fetal requirement for folic acid exceeding the dietary intake, but impaired absorption of this vitamin during pregnancy may also play a part. The rate of clearance of folic acid from the plasma was even more rapid in patients with megaloblastic anemia of pregnancy. The high incidence of this anemia in women with twin pregnancy and its onset in late pregnancy suggest that the factors producing folic-acid deficiency in women with normal pregnancy are responsible for the more severe folic-acid deficiency in patients with megaloblastic anemia. Since the absorption of folic acid appeared to be most impaired in the patients with megaloblastic anemia, this may contribute to the development of the more severe grade of folic-acid deficiency found in these patients. The dietary intake of folic acid may also be important.

Nonfatal Pulmonary Amniotic Embolism: An Unusual Transplacental Path of Entry. L. P. Cawley, R. C. Douglass and C. L. Schneider. Obst. & Gynec. 14:615-620 (Nov.) 1959 [New York].

A multiparous 37-year-old woman, with a 10-year history of neurosyphilis and of psychosis, was transferred to the Wayne County General Hospital in Eloise, Mich., with recurring grand mal seizures associated with a "term pregnancy one week before delivery." Pulmonary *amniotic fluid embolism* was diagnosed post partum from the symptoms of dyspnea, orthopnea, hypotension, cyanosis, hemoptysis, elevated venous pressure, and transient sequential roentgenographic and electrocardiographic changes. The diagnosis was supported by the observation of heavy soiling of the amniotic fluid with meconium and the finding of a transplacental channel which could have provided a ready pathway for entry of amniotic fluid into the maternal circulation. Six months after delivery the patient died of an intercurrent disease. No residual traces of pulmonary emboli, of amniotic debris, or of pulmonary vascular sclerosis were found at autopsy. These observations suggest that such debris is subject to phagocytic action and histolytic digestion with resolution of the vascular occlusions, thus leaving little or no late traces that are demonstrable histologically. Clinically, there was mild transient "obstetric shock," and this is adequately accounted for by the production of acute cor pulmonale by disseminated pulmonary embolism of formed debris from amniotic fluid.

The Use of a Tranquilizer Drug in Childbirth. E. W. Lander. Southwestern Med. 40:704-705 (Nov.) 1959 [El Paso, Texas].

Prospective mothers should be taught that there is nothing pathological about normal labor and that complications are exceptional. The naturalness of childbirth should be stressed, with the idea of eliminating on minimizing fear. A simple explanation of the mechanism of labor, what the patient may expect and what will be expected of her, may be interjected at visits during the third trimester.

A mother should be permitted to have her baby with no anesthesia, except for complicating circumstances which dictate the procedure. The use of general anesthesia for the actual delivery is all too often the desire of the physician rather than the patient.

The action of certain of the tranquilizer drugs is ideal in obstetrics, in that they induce relaxation and tend to minimize the fear of labor. The phenothiazine derivatives, such as chlorpromazine and promazine, have been used successfully, but with occasional undesirable complications. Perphenazine (Trilafon) is one of the newer drugs in this category which, in therapeutic dosage, is relatively free of toxicity; at the same time, it is 5 to 10 times more potent. The author used Trilafon chiefly in primiparas but also in multiparas with histories of hard labor or long interval since last childbirth. One 8-mg. tablet of Trilafon was given orally, usually on admission to the hospital, although a few multiparas have been given a tablet beforehand, to be taken at home as soon as they felt that labor has started. The serenity and composure of these patients during labor have been striking. On being questioned 24 hours post partum, they were all uniformly pleased with their labor experience. Moreover, there have been no visible adverse effects on the newborn infant. The use of additional analgesia has been minimized during childbirth. The majority of women received only one injection, consisting of Nisentil (30 mg.) and Lorfan (0.5 cc.) in the terminal phase of the second stage. The majority have delivered spontaneously without any further anesthesia or with only a few whiffs of Trilene.

Fetal Death in Utero. J. A. Pritchard. Obst. & Gynec. 14:573-580 (Nov.) 1959 [New York].

The author delineates a regimen for managing the patient with intrauterine retention of a dead fetus. Observations on 100 women with a dead fetus which had been retained for one or more weeks indicate that the patient is unlikely to develop potentially dangerous hypofibrinogenemia in less than 5 weeks after the fetal death. However, one out of 4 women who retained a dead fetus in utero for 5 or more weeks developed potentially dangerous hypofibrinogenemia. Hypofibrinogenemia, prior to delivery, may be asymptomatic, or there may be clinical evidence of abnormal hemostasis. Fibrinogen administration without emptying the uterus results only in a transient elevation of the level of circulating fibrinogen. The administration of fibrinogen may not infrequently result in homologous serum hepatitis. Labor, either spontaneous or induced with oxytocin, does not result in further fibrinogen depletion. A number of patients who carry a dead fetus in utero for a prolonged period of time develop anxiety states, which cause considerable distress and have been difficult to eradicate completely. It is recommended that the patient with a dead fetus be observed for 3 or 4 weeks after the fetal death. During this time she will probably go into labor and deliver without difficulty. If she has not delivered at the end of this period, the uterus should be evacuated.

DERMATOLOGY

The Disease Called "Wildfire." C. E. Counter. A. M. A. Arch. Dermat. 80:391-397 (Oct.) 1959 [Chicago].

The author reports on 47 consecutive patients with a disease closely resembling exfoliative pemphigus, who were admitted to the Pemphigus Hospital of Mato Grosso, Brazil. The Brazilian expression "fogo selvagem," applied to this endemic disease of central South America, literally means uncontrolled fire, in much the same way that the word "wildfire" brings to mind a fire that has got out of control in dry grass. The patients truly experienced a burning feeling that continued uncontrolled for days and months; only when they were completely quiet did they get any degree of relief. The patients were between the ages of 10 and 30 years when the symptoms began, and the disease might last 15 years or longer. Typically, the first lesion was a vesicle on the central part of the face or on the upper part of the chest; other vesicles and bullae soon developed over the face and upper trunk; often lesions involved the whole trunk and the extremities and even the scalp. Mucous membrane surfaces lining the various orifices were not involved. As the bullous lesions became more numerous and extensive, an exfoliative dermatitis developed. There was a distinct odor of dried serum, which was the distressing repulsive feature of the disease. Of the 47 patients, the disease was subacute in 2, chronic in 43, and ill-defined in 2. In the 43 patients with chronic disease, the disease was further classified as bullous exfoliative in 24, pustular and ulcerative in 5, intensively foliaceous in 9, herpetiform in 2, verrucous in 2, and hyperpigmented in 1.

Treatment of this odd disease with quinacrine hydrochloride given orally produced regressions in 87 (58%) of 151 patients treated at the Instituto Ademar de Barros in Mandaqui, São Paulo, Brazil. Quinacrine is known to produce improvement in diseases showing intolerance to sunlight, such as chronic discoid lupus erythematosus and polymorphic light-sensitive eruption. The treatment of the patients in the Pemphigus Hospital of Mato Grosso consisted chiefly of hydrotherapy followed by the application of a tar preparation. Repeated 3 times a week, it brought about a rather permanent arrest of the disease. At least 56.5% of the patients treated with the tar preparation had their disease arrested or improved sufficiently to be treated at home and to obtain their complete arrest of pemphigus. The patients seemed to value the relief from itching and from the odor even more than the cure possibilities. It may be that the chief value of baths and tar-compound applications for patients with the Brazilian type of pemphigus foliaceus is its ability to produce hyperpigmentation.

Clinical Features of Contact Dermatitis Due to Neomycin: Report of Cases. H. Reynolds, J. F. Hildebrand, C. S. Livingood and R. P. Fosnaugh. A. M. A. Arch. Dermat. 80:455-460 (Oct.) 1959 [Chicago].

The authors report on 10 male and 18 female patients, between the ages of 5 and 65 years, in whom a diagnosis of contact dermatitis due to neomycin was made. With the exception of 3 patients, the development of neomycin sensitivity was an insidious process. In these 3 patients there was a definite correlation between the use of a neomycin-containing preparation and the onset of an acute exacerbation. Most of the other patients were suspected of neomycin sensitivity because of a gradual progression of their eruption and failure to respond to what would be considered adequate therapy. In this group there was no clear-cut relationship between use of a neomycin-containing preparation and progression of dermatitis. The use of neomycin did not cause an acute exacerbation. In 2 patients, one with an eczematous dermatitis and the other with otitis externa, the use of a neomycin-containing topical preparation caused an exacerbation, which was interpreted at the time as being a flare-up of the underlying dermatitis.

An analysis of the primary sites of involvement, including feet, ears, hands, axillas, eyelids, and perianal region, would seem to support the clinical impression that sensitization may be more apt to occur if the involved site is an intertriginous area, or subject to maceration. However, the predominance of otitis externa (in 9 of the 28 patients) may only be a reflection of the widespread use of neomycin-containing topical steroids in this situation and chronicity of the problem. It is felt that neomycin contact sensitivity is not common. The onset may be insidious, and despite an increased index of suspicion on which recognition depends, rather than on the appearance of the classical signs of acute contact dermatitis, only 3 cases have been observed by the authors in the past. The possibility of such sensitivity should, however, be borne in mind, especially in a patient with an eczematous dermatitis, who is using a neomycin-containing preparation and who is not responding satisfactorily. In all the patients, symptoms and signs regressed promptly after withdrawal of neomycin.

UROLOGY

Analysis of 51 Patients with Horseshoe Kidney. J. F. Glenn. New England J. Med. 261:684-687 (Oct. 1) 1959 [Boston].

Horseshoe kidney is one of the more common congenital urologic anomalies, occurring once in every 400 or 500 births. The literature deals mainly with the surgery and with the various grave complications secondary to the anomaly, but fails to reveal any adequate long-term follow-up study of patients with horseshoe kidney. The author studied 51 consecutive patients (28 males and 23 females) with horseshoe kidney seen at Duke Hospital, Durham, N. C., over a 25-year period, 1933 to 1958. Pain or signs of urinary-tract infection were the predominating symptoms. Horseshoe kidney was an incidental finding in almost a fourth of the patients. The initial diagnosis was made radiologically in 82.3%, at autopsy as an incidental finding in 11.8%, and clinically in 5.9% (with subsequent radiologic confirmation).

Thirty-one patients were followed for from 1 to 22 years (an average of nearly 10 years); the remaining patients had died (6) or were lost to follow-up. Eighteen of those followed for prolonged periods remain asymptomatic and without complications at this time. Five of the other 13 patients are known to have renal calculi, 4 have persistent infection, and 4 have Rovsing's syndrome (nausea and vomiting and abdominal pain accentuated by hyperextension). The long-term follow-up indicates that the complications of infection may be controlled by conservative measures in many cases. Hydronephrosis and calculus formation were quite common and were the indications for surgical treatment in 12 of the patients. Successful surgery depends upon correction of the anatomic deformity by division or resection of the isthmus, nephropexy, and pyeloplasty. Surgery for relief of pain has been condemned, and was not utilized in any of these patients. While horseshoe kidney is thought to occur more commonly in young persons, the patients in this series, at the time of diagnosis, were of an average age of 34 years, and only 7 were less than 7 years old.

Tumors of the Renal Pelvis: Review of Sixty-Four Cases. A. B. Seth-Smith. Brit. J. Urol. 31:265-276 (Sept.) 1959 [Edinburgh].

This report is based on the records of 64 patients with primary tumor of the renal pelvis, treated at the London Hospital during the 48 years up to December, 1956. Full clinical information is lacking in a few cases. Fifty patients underwent surgical treatment of some kind, the condition of the remainder being either too advanced for such treatment or undiagnosed during life. The group included 12 cases of papilloma without invasion or cellular malignancy; 23 cases of papillary carcinoma, in 4 of which there was no invasion, while 19 showed local or general spread; and 29 cases of solid carcinoma. The high incidence of solid infiltrating growth (45%) was unusual, because these tumors, particularly the squamous-cell ones, are becoming less common. In contrast, 5 out of 12 cases of papilloma occurred in the last 6 years under review. The papillary growths which show no evidence of malignancy have been grouped separately, and it is suggested that the prognosis may be relatively favorable in this group. Results of treatment in the other groups are largely disappointing, and among those with solid tumors no 5-year survivals are to be found. Only on very few occasions was primary nephroureterectomy done, and it is possible that this affected the prognosis badly in some of the cases.

It is generally accepted that these tumors cannot be differentiated from one another with any degree of accuracy by histological examination. Solid growths may be composed of transitional, spheroidal, columnar, or squamous cells, alone or in combination, and those which appear papillary on the surface frequently contain areas of squamous-cell carcinoma. Classification, therefore, is bound to be somewhat arbitrary and should be restricted to broad outlines. However, differentiation between papillary and nonpapillary tumors has stood the test of time, and now there is no doubt that the papillary tumors carry a better prognosis. Nevertheless, the contention that squamous and papillary tumors are entirely unrelated appears to be misleading. There are many similarities between tumors of the bladder and those of the renal pelvis; yet in the bladder the papilloma is usually kept separate from the more malignant tumors, because the outlook after treatment is relatively favorable. Bladder papillomas can grow to great size without being considered malignant. It is interesting to speculate whether urinary carcinogens are a factor in producing tumors of the mucous membrane with which they come into contact, but there is as yet little evidence of this. Bilateral tumors occurred once in this series, but they are remarkably rare. In this series, calculi were present in almost half of the cases of solid tumor and in 1 out of 7 of the papillary ones, a similar incidence to that reported by others. Renal anomalies, stasis, infection, and calculi may play a part in causing papillary as well as squamous tumors.

Torsion of Testis. G. Fahlström and H. Johansson. Nord. med. 62:1486-1487 (Oct. 8) 1959 (In Swedish) [Stockholm].

Torsion of the testis, most frequent before the age of 20 years, is an acute surgical disease requiring attention within the first hours. Testes in the scrotum are affected as often as undescended testes. Intracapsular torsion, often bilateral, depends on a malformation which allows the testis increased motility; extracapsular torsion is, as a rule, due to trauma, and here no other malformation than possible retention of the testis is a contributing factor. The onset is usually marked by acute pain, localized in the affected testis, often almost like kidney colic, sometimes with vomiting. In cases with less pronounced pain, diagnosis is more difficult. Eight cases are described in patients, aged from 2 to 19 years. In 3 of these, exploration revealed a gangrenous testis; in one case exploration resulted in the diagnosis of epididymitis. In 2 of the 4 patients treated surgically, operation was delayed because of mistaken diagnosis; in both patients there was disturbance of nutrition, with gangrene. The prognosis depends on how intensive the nutritional disturbance is and how early surgical treatment is instituted. The difficulty in diagnosis justifies exploration in uncertain cases. The most frequent mistaken diagnosis is that of acute epididymitis. Irreversible changes occur in testicular torsion after a short period of strangulation.

Kidney Transplantation from a Nonidentical Twin to Another After Irradiation of the Entire Body of the Recipient: Satisfactory Kidney Function Four Months After Transplantation: Preliminary Report. J. Hamburger, J. Valysse, J. Crosnier and others. Presse méd. 67:1771-1774 (Oct. 17) 1959 (In French) [Paris].

The authors report a 37-year-old man with chronic disease of the kidneys which had progressed to terminal renal insufficiency. The man was given 2 sessions (6 days apart) of cobalt radiation of the entire body with a total dose of 460 r. The day after the second radiation treatment the transplantation of the kidney on the left side was performed. The donor was the twin brother of the recipient. The nonidentical characteristics of the 2 brothers were established by clinical and biological findings. The patient was kept in a strict aseptic environment, beginning the day of the first radiation, for a period of one month in order to avoid infection during the phase of aplasia of the blood and the bone marrow due to cobalt radiation. During the first 15 days after the operation, the function of the transplanted kidney was satisfactory. In the third week a sudden critical period of renal insufficiency occurred. This subsided in the fourth week, with return to normal renal function, disappearance of signs and symptoms of uremia, and disappearance of the retinal lesions. Four months after the kidney transplantation the general condition of the patient was excellent.

The factors which may have played a part in the success of the transplantation are: (1) the condition of chronic renal insufficiency of the recipient;

(2) the radiation treatment; and (3) the close relationship between the donor and the recipient. The hypothesis of a synergic action of these factors is advanced as a possible explanation of the success. Perhaps the critical period in the third week after transplantation may be interpreted as the first recovery from the immunological disease which usually provokes the rejection of the transplant. If the idea is correct that this disease is not irreversible, new prospects are opened in the field of kidney transplantation.

Some Common Complications After Prostatectomy. J. C. Ross and L. F. Tinckler. Brit. M. J. 2:663-666 (Oct. 10) 1959 [London].

While postoperative complications have always developed in a certain percentage of patients undergoing prostatectomy, now, with the increasing age of the patients and the number who have intercurrent medical conditions, these are likely to become more frequent. The authors investigated complications arising in 100 prostatectomies, the patients being unselected. Wilson Hey prostatectomy was carried out in 65 cases, retropubic prostatectomy in 3, and cold-punch resection (perurethral) in 32. The type of operation apparently makes no essential difference as to the incidence of complications. With modern methods of anesthesia, the danger period of prostatectomy has shifted from the actual operation to the first few postoperative weeks. The authors are not concerned with immediate or reactionary hemorrhages, as modern operations, including perurethral resection, appear to cope fairly successfully with hemorrhage. Osteitis pubis did not develop in any of the patients. The postprostatectomy flap or valve is rarely encountered now that operation is carried out under direct vision and trigonectomy is performed.

A temporary incontinence was noted in approximately a quarter of the present series. A simple method of "sphincterometry" was used in the assessment of this incontinence. Postmeatal stricture appears to have been largely eliminated by discarding the red rubber catheter. With the use of a latex catheter, a urethral stricture developed in only 2% of the patients. Postoperative infection continues to be the most obstinate problem, Escherichia coli and Proteus vulgaris preponderating. It is suggested that back-pressure and hydronephrosis before operation are factors in encouraging infection. It is also pointed out that the peak period of infection occurs during the first 4 weeks, during which the prostatic cavity is in the process of epithelizing. The incidence of epididymitis with vasostomy was 7% in this series. A temporary suprapubic leak occurs in a proportion of patients, and is probably due to a lack of healing ability in elderly and debilitated patients.

THERAPEUTICS

Treatment of Pemphigus Foliaceus with Triamcinolone: New Personal Cases. T. A. Furtado and G. Batista. Hospital 56:657-664 (Oct.) 1959 (In Portuguese) [Rio de Janeiro].

Three patients with pemphigus foliaceus obtained complete regression of their lesions with triamcinolone, and the authors accordingly applied the same therapy to another 10 patients. The latter included 9 women and 1 man, between the ages of 10 and 28 years, except for one who was 43 years old. The cutaneous manifestations and the general condition in 7 patients were pronounced. There was impairment of joint function, intense sensation of burning, and pruritus. The shortest duration of the disease was 1 month; the longest was 10 years. Triamcinolone was given in an initial dose of 32 mg. daily to 7 patients, and of 16, 36, and 48 mg., respectively, to the other 3. The total dose administered varied between 180 mg. and 2.88 Gm., and the daily maintenance dose ranged from 4 to 8 mg.

Within a period of 34 to 166 days all 10 patients obtained clinical recovery, including improvement in the general condition and, in some patients who had become amenorrheic, return of the menstrual cycle. No relationship was found between duration of the disease and response to treatment, although the generalized forms with intense bullous, exfoliative lesions required a higher daily dosage. Reduction of the dose to a maintenance amount of 4 to 8 mg. was possible in a short time. Although some patients had a relapse during the treatment, no recurrence was observed after clinical recovery had been achieved. The drug was well tolerated. Only one patient developed a "full-moon face." A second patient manifested a mild euphoria. The authors believe that triamcinolone is the choice corticosteroid for treatment of pemphigus foliaceus. Although the effect is palliative and not curative, the administration of small maintenance doses permits the patients to remain free from symptoms and to resume a normal life.

Treatment of Progressive Protopathic Muscular Dystrophy with Group-Specific Extracts Derived from the Gastric Mucosa of Hogs. B. Manzini and L. Frattola. Minerva med. 50:3240-3242 (Oct. 13) 1959 (In Italian) [Turin, Italy].

The authors report on the effect of some group-specific extracts derived from the gastric mucosa of hogs on 21 patients, 3 female and 18 male, 10 to 52 years of age, with progressive protopathic muscular dystrophy. The extracts, which contained both a nonacid polysaccharide and an amino acid, were administered in tablets of 100 mg. each, 2 to 3 tablets per day, to each patient for a period of one month. The extracts had a beneficial effect on the kinesthesis of each patient. In some patients the muscular strength improved; one patient, who before the treatment had to interrupt his work every 20 to 30 minutes, after 20 days of treatment was able to do manual work uninterruptedly for longer periods of time; another patient was able to change from a sitting position to a standing one with the need of no support; a third patient, in the last phase of the treatment, was able to walk without falling, as used to happen before the treatment. The body weight increased in all but one patient who during the treatment suffered from bronchopneumonia. The values of the aldose activity of most patients declined to below normal. The decline was already present during the first days of treatment. Tests made in 5 patients 3 months after the treatment showed that the aldose values had increased again and that in 3 patients they were higher than the values recorded at the beginning of the treatment; loss of body weight was also noticed at this time. The transaminase values, checked in 14 patients, increased moderately after the administration of the extracts but with no apparent relationship to the course of the disease. The authors believe that progressive protopathic muscular dystrophy may be related to an early deficiency of anabolic endogenous factors.

Therapeutic Value of Sulfamethoxypyridazine in Some Internal Infections. A. Legramante and A. Perrone. Minerva med. 50:3237-3239 (Oct. 13) 1959 (In Italian) [Turin, Italy].

The authors report on the effect of sulfamethoxypyridazine on 71 patients with infection of the urinary tract or of the respiratory tract, on 10 patients who had previously suffered from rheumatic disease and were in need of antistreptococcic prophylaxis, and on 48 patients to whom the drug was given prophylactically before tonsillectomy, tooth extraction, and lymph node, kidney, or liver biopsy. A dose of 2 to 3 Gm. of sulfamethoxypyridazine was given on the first day, and a dose of 1 to 1.5 Gm. the following days. The drug was well tolerated. The patients with bronchopulmonary or urinary infections received the drug in combination with antibiotics, and the results obtained were rapid and good. Good results were obtained in 30 of 32 patients with severe pharyngotonsillar infection; 28 of these patients were treated with the sulfonamide only, one with the sulfonamide combined with tetracycline, and one with the sulfonamide combined with penicillin. Good results were also obtained in patients with chronic bronchitis who suffered from acute relapses and in patients with bronchiectasis. In patients with acute infections of the urinary tract, the drug was effective not only on gram-positive and gram-negative cocci but also on Escherichia coli and at times Pseudomonas aeruginosa.

Among 53 patients with urethritis, cystitis, and pyelonephritis, sulfamethoxypyridazine had a beneficial effect on 17 patients in whom the disease was caused by Esch. coli; these 17 patients, especially those with pyelonephritis, received the drug for more than 10 days. The drug had no effect on 6 of the remaining 36 patients; 2 were suffering from urethritis caused by Staphylococcus albus, 3 from cystitis and pyelonephritis due to Proteus organisms, and 1 from cystitis caused by Ps. aeruginosa. Good results were also obtained in those patients in whom sulfamethoxypyridazine was used as an antistreptococcic prophylactic of rheumatic disease or for general anti-infective prophylaxis before tonsillectomy, tooth extraction, or biopsies. In patients with rheumatic disease the administration of the drug was followed by a progressive decline, and in some cases even the disappearance, of the serum values of antistreptolysin.

First Clinical Research on the Anticholesterol and Antilipid Effect of a New Estrogen Derivative: 16-α-Chloroestrone 3-Methyl Ether. G. Annoni. Minerva med. 50:3084-3088 (Sept. 29) 1959 (In Italian) [Turin, Italy].

Some halogenated derivatives of estrone have a marked lipid reducing effect and a low estrogen effect; most active among these derivatives are those which are obtained by introducing an atom of iodine or chlorine in the 16-alpha position. The author reports on the effect of one of these derivatives, 16-alpha-chloroestrone 3-methyl ether, on 15 arteriosclerotic patients. Eight patients (3 male and 5 female) suffered from diffuse arteriosclerosis; 3 (2 male and 1 female) from myocardiocoronary arteriosclerosis; 2 (1 male and 1 female), from cerebral arteriosclerosis; and 2 (1 male and 1 female), from arteriosclerosis mainly of the lower limbs. Each patient received 5 mg. of the drug per day, given in 2 equal subdoses; the treatment lasted from 20 to 30 days. Results of laboratory tests showed a 15 to 40% decline in the level of total serum cholesterol in all but 2 patients. This decline was similar in the ester fraction and in the free fraction, in men as well as in women, and was more marked the higher the initial value of the cholesterol level; a 20 to 30% decline was observed in 9 patients.

The decline of the cholesterol level was already manifest on the 10th day of treatment and became most marked after 20 to 30 days of treatment. The cholesterol values tended to increase, though slowly, when the drug was withdrawn, and in 2 or 3 months they were comparable to the values recorded at the beginning of the treatment. One of the 2 patients whose serum cholesterol level was not affected by the drug was a 30-year-old obese man with diffuse arteriosclerosis; his father, too, presented high cholesterol and lipid values, and suffered from severe arteriosclerosis and diabetes. The second patient was a 60-year-old woman with arteriosclerosis and biliary calculosis of the cholesterol type. The drug in this instance had to be withdrawn after 20 days of treatment because of the recurrence, after 10 years, of a mild menstrual flux, which disappeared in 3 days. With the exception of these 2 patients, the values of total lipemia declined from 15 to 25% in all instances. The clinical results, though nothing definite can be said yet, were also good. The physical and psychointellectual conditions of the patients improved. With the exception of the 2 persons who derived no benefit from the drug, no other patients showed intolerance.

The author believes that the mechanism of action of 16-alpha-chloroestrone 3-methyl ether is not the same as that of the synthetic anticholesterol drugs derived from acetic acid. The undoubted anticholesterol effect of the drug is more marked than the antilipid effect. The drug has also an estrogenic effect that may become manifest clinically.

Hypercoagulation in the Course of Treatment with Anticoagulant Drugs. R. Raynaud, M. Brochier and A. Tadei. Presse méd. 67:1733-1734 (Oct. 10) 1959 (In French) [Paris].

Three types of hypercoagulation, "resistant," "provoked," and "dissociated," which were observed in some patients who were being treated with anticoagulant drugs, such as heparin or bishydroxycoumarin (Dicumarol), are discussed. The cases of 2 patients with resistant hypercoagulation —the first, a 35-year-old woman with mitral disease, who did not respond to heparin given by continuous perfusion in a dose of 500 to 600 mg. per day, and the second, a 45-year-old man, who had suffered repeatedly for 5 years from phlebitis and who did not respond to a large dose (1.050 mg.) of ethyl biscoumacetate (Tromexan Ethyl Acetate), to heparin, or to both drugs given in combination —are presented. The authors believe that thrombophilia in these 2 patients was due to the presence of an excessive amount of thromboplastin and platelets in the blood; coumarin derivatives have very little effect in such instances. Good results can be obtained, however, as was shown in a third case reported, if heparin is associated with Dicumarol or if the dose of Dicumarol is increased. It was observed in this third patient that at a certain moment the hypercoagulation "let down," and then it was possible to withdraw heparin.

Provoked hypercoagulation may occur either as the result of a faulty anticoagulant treatment or in the course of a nonfaulty treatment. The case of a patient, 78 years of age, in whom hypercoagulation was provoked by the withdrawal of heparin, which was to be substituted with Dicumarol, is presented. The condition of this patient improved as soon as the heparin therapy was reinstituted. A faulty treatment, in cases of patients who are receiving Dicumarol only, may be the result either of a too high initial dose or of the sudden withdrawal of the anticoagulant. The cases of 2 patients, 50 and 18 years of age, respectively, who suffered from provoked hypercoagulation despite a nonfaulty treatment, are presented. This form of hypercoagulation is observed almost exclusively during treatment with coumarin derivatives. In these 2 patients at first the prothrombin values, the heparin test, and even thromboelastography indicated good hypocoagulation; in a few days, however, the results of the tests and especially of thromboelastography became less satisfactory, indicating that the treatment had provoked hypercoagulation. In the latter case it seemed that the coumarin derivatives provoked, paradoxically, [illegible] nd that they neutralized the [illegible] of heparin.

The last form of hypercoagulation in the course of treatment with anticoagulant drugs, dissociated hypercoagulation, is evidenced by a dissociation between the results of the prothrombin values and of the heparin tolerance test or of the thromboelastogram, as well as dissociation between the vertical and horizontal data of the thromboelastogram. The authors believe that only thromboelastography can give reliable evidence of the effect of treatment with anticoagulants in patients with progressive thrombosis, and of the possible appearance of thromboembolic accidents in the course of properly carried out treatment with anticoagulants.

PATHOLOGY

Isolation of Measles Virus at Autopsy in Cases of Giant-Cell Pneumonia Without Rash. J. F. Enders, K. McCarthy, A. Mitus and W. J. Cheatham. New England J. Med. 261:875-881 (Oct. 29) 1959 [Boston].

Giant-cell pneumonia, often referred to as Hecht's giant-cell pneumonia, is an interstitial pneumonitis that has so far been observed only in children. It is characterized by the presence of multinuclear giant cells with intranuclear and intracytoplasmic inclusion bodies. Additional pathological features are a preponderance of mononuclear cells in the infiltrate, squamous metaplasia of the bronchial and bronchiolar epithelium, proliferation of alveolar lining cells, and the occurrence in occasional cases of giant cells in organs other than the lungs. The etiological agent has remained obscure. No bacterial species has been found causally associated with the pneumonic process. The viruses of canine distemper and measles have both been suggested, principally because they induce the formation of giant cells with characteristics resembling those present in this type of pneumonia.

The authors report observations on 3 girls, 2 to 4 years of age, who were admitted to the Children's Hospital in Boston with chronic debilitating diseases. The diagnosis of giant-cell pneumonia was made restrospectively upon histological examination of lung tissue obtained at autopsy. The chronic diseases existing in these children were mucoviscidosis, leukemia, and Letterer-Siwe disease respectively. None of the children had signs or symptoms of measles during their illnesses, although one of them had been exposed to 2 siblings with measles.

The evidence presented appears to justify the conclusion that the viruses isolated post mortem from pulmonary secretions or tissue of 3 typical cases of giant-cell pneumonia (Hecht) are indistinguishable from the virus of measles. The evidence consists of similarity or identity of cytopathogenic properties, growth characteristics, infectivity for macaco monkeys, lack of pathogenicity for suckling mice and chick embryos, and antigenic composition. It, therefore, seems justifiable to conclude that measles virus was the etiological agent in the 3 cases of giant-cell pneumonia. Although this number is small, the authors believe that it is sufficient to indicate that, in at least a proportion of cases of giant-cell pneumonia, measles virus will prove to be the responsible agent.

Persistence of Measles Virus and Depression of Antibody Formation in Patients with Giant-Cell Pneumonia After Measles. A. Mitus, J. F. Enders, J. M. Craig and A. Holloway. New England J. Med. 261:882-889 (Oct. 29) 1959 [Boston].

The authors present the results of studies on 4 leukemic children with measles complicated by severe pneumonitis. From 2 of these patients with pneumonitis that followed the subsidence of signs of measles, agents identified as measles virus were isolated. The virus was also recovered from tissues taken at autopsy. The diagnosis of giant-cell pneumonia was made provisionally during the course of the illness and confirmed after death. Measles virus persisted for an unusually long period in the upper respiratory tracts of these patients, who also failed to respond in the normal manner by development of specific antibodies. The clinical and pathological features of the pneumonitis were indistinguishable from those found in the patients described in the preceding paper, with giant-cell pneumonia not associated with overt measles.

In the other 2 patients with pneumonitis after measles who survived, measles virus was found to persist for unusually long periods in one, and the antibody response appeared to be depressed in both. Accordingly, it is probable that giant-cell pneumonia was also present in these 2 children. Laboratory diagnostic methods now available permit the clinical recognition of giant-cell pneumonia caused by measles virus. To make this diagnosis appears important, especially regarding therapy and prevention. Since the 2 surviving patients in this study received large quantities of measles antibody, it is possible that seroprophylaxis and serotherapy will prove effective. The survival of 2 patients who received large doses of gamma globulin at the time of exposure suggests that this material may be of value in modification of subsequent measles pneumonitis. Furthermore, it is possible that very large quantities of antibody administered intravenously in the form of measles convalescent plasma will mitigate this condition, since rapid recovery in one case followed this procedure. Abnormal responses on the part of leukemic children to infection with measles is also of interest.

Chronic Pyelonephritis Lenta and the "Malignant Phase of Hypertension." O. Saphir and N. A. Cohen. A. M. A. Arch. Int. Med. 104:748-762 (Nov.) 1959 [Chicago].

The authors report on 25 Negro and 10 white patients, between the ages of 29 and 78 years, with the malignant hypertension syndrome, who died in the Michael Reese Hospital, Chicago, and whose autopsy protocols have been reviewed with special reference to gross and microscopic changes in the kidneys. In contrast to previous autopsy reports in the literature, in which the kidney lesions of most patients with malignant hypertension were ascribed to "malignant nephrosclerosis," the authors emphasize that malignant nephrosclerosis as one pathological entity does not exist. By means of established criteria, a diagnosis of pyelonephritis lenta was made in 27 of the 35 patients, and a diagnosis of glomerulonephritis combined with pyelonephritis lenta was made in the remaining 8 patients. By pyelonephritis lenta is meant, in contrast to destructive pyelonephritis, a slowly developing inflammation of the kidney involving principally the pelvis, tubular apparatus, and interstitial tissue, in the absence of suppuration. Most likely, because of the involvement of the interstitial tissue, the arteries of the size of the intracortical and arcuate vessels become secondarily affected, in the form of an endarteritis deformans with severe narrowing of the lumen. As in Goldblatt's experiments, these changes are probably responsible for the hypertension.

The clinical aspects of the 27 patients with pyelonephritis lenta were notable in that most of them were without a clinical history of typical or classical pyelonephritis. However, in 2 patients who had been previously hospitalized for diverse reasons, there was unequivocal laboratory evidence of urinary tract disease long before the onset of hypertension. In contrast, the 8 patients in whom glomerulonephritis was one factor in the picture of malignant hypertension generally had clinically known long durations of renal disease before the onset of hypertension. These findings show that the clinical course of pyelonephritis lenta is insidious, often silent ("lenta"), until the severity of the lesions of the blood vessels causes hypertension. The cause of pyelonephritis lenta and whether or not it is blood-borne or "ascending" are not known. Most likely the disease is the result of an insidious bacterial infection spreading to the interstitial tissue of the kidneys. The malignant phase is ushered in by a superimposed element appearing either very early or late. Impending myocardial failure, glomerulonephritis, acute pyelitis, acute pyelonephritis, infarcts of the kidney, or chronic progression of the intrarenal changes, proceeding to a stage responsible for renal failure, may constitute this second factor. Arteriolar necrosis cannot possibly usher in the malignant phase, since it is obviously a very recent phenomenon, occurring only after renal failure has been established.

Thoracic Choriocarcinomas. P. Thibault. Presse méd. 67:1892-1895 (Oct. 31) 1959 (In French) [Paris].

Choriocarcinomas are either primary and mediastinal or, more often, metastatic and pulmonary. They occur in both women and men. In women, they are gestational or nongestational. In men, they probably represent a nonabsorbed or undeveloped puberal element that under some hormonal stimulation develops into a tumor. The development of gestational choriocarcinomas usually occurs in the weeks after a mole, a nonmolar abortion, or even an apparently normal delivery. As the neoplastic elements migrate through the blood, the lungs form their first barrier, and pulmonary metastases occur in almost 100% of the patients. Cough, extensive and frequent hemoptysis, and roentgenologic findings of round, multiple, and bilateral pulmonary images are characteristic signs of pulmonary metastases which occur within a short interval after the gynecologic manifestations. These signs and symptoms, together with a high rate of prolan B, indicate nearing death even if the pulmonary nodules may regress. Nongestational choriocarcinomas in women are secondary to an ovarian embryoma. They usually occur between the ages of 14 and 23 years. Abdominal pain and hormonal manifestations, such as metrorrhagias, acceleration of puberal development, menstrual disorders, excessive urinary gonadotropins, and positive Aschheim-Zondek reaction, are the main symptoms. In some exceptional cases the origin may be epiphysial. The pulmonary signs and symptoms as well as the fatal course of these tumors are similar to those of the gestational choriocarcinomas.

All the mediastinal choriocarcinomas reported to date have occurred in men, with one exception only. These tumors are usually observed in men, between the ages of 15 and 35 years. The intrapulmonary forms are almost always secondary. The intramediastinal forms are almost always primary and have a complex dysembryonic structure in which the choriocarcinomatous element is only one of the components. Approximately 130 cases of thoracic choriocarcinomas in men have been reported—102 pulmonary and 28 mediastinopulmonary. The pulmonary type is the result of an early blood afflux from a partially or entirely carcinomatous focus. The original focus was testicular in 67 of the 102 patients reported, mediastinal in 21, and epiphysial in 1. The mediastinal choriocarcinoma is usually a heteroplastic dysembryoma. Besides the symptoms observed in women with these tumors, in men the mediastinal or the mediastinopulmonary forms include a syndrome of compression of the superior vena cava with hemorrhagic or serous pleural exudation. Together with the other symptoms of thoracic choriocarcinomas, there is often an effemination syndrome with gynecomastia, testicular atrophy, and a high rate of prolan B. The course is even more rapid in men than in women and does not show any regression. No effective therapeutic approach to choriocarcinoma has been found, as many histogenic, biological, and etiological problems are still unsolved.

Examinations of Atypical Mycobacteria: Comparative Bacteriological Examinations Concerning Identification and Classification into Groups. G. Meissner. Beitr. Klin. Tuberk. 120:377-387 (No. 6) 1959 (In German) [Berlin].

Bacteriological examinations of 80 strains of atypical mycobacteria were carried out in order to identify them and to differentiate them from the known human and bovine strains of tubercle bacilli, and to classify them into 4 different groups. Drug-susceptibility tests with isoniazid, streptomycin, aminosalicylic acid, and amithiozone (Conteben) proved to be very useful in the identification of atypical mycobacteria. The atypical acid-fast bacilli are more resistant to chemotherapy than the human and bovine tubercle bacilli obtained from untreated patients. The atypical mycobacteria can also be differentiated from the human and bovine tubercle bacilli by the positive peroxidase reaction of cultures grown on a medium containing isoniazid in a concentration of from 10 to 50 mcg. per milliliter, as well as by a negative niacin test. The examination of cultures on Löwenstein-Jensen egg medium and on 5% glycerol agar at different temperatures makes it possible to classify the mycobacteria into the following 4 groups: (1) photochromogenic; (2) scotochromogenic; (3) avian and avian-like; and (4) "fast-growing," generally considered saprophytic.

BOOK REVIEWS

The Acute Radiation Syndrome: A Medical Report on the Y-12 Accident, June 16, 1958. Compiled by Marshall Brucer. From Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, under contract with United States Atomic Energy Commission, Technical Information Service. Work performed under contract no. AT-40-1-Gen-33. ORINS-25, biology and medicine. Paper. $1. Various pagination, with illustrations. Office of Technical Services, Department of Commerce, Washington 25, D. C., 1959.

In a series of 13 laboratory and clinical studies made on five persons who were accidentally exposed to whole body radiation of large doses of radiation at Oak Ridge, Tenn., additional information concerning the clinical, hematological, and biochemical changes after exposure is described in detail. The five persons, each exposed to 200 to 300 rads, were hospitalized immediately. Extensive studies were begun at once and continued until the patients were discharged. Three additional persons who received doses of 70 to 20 rads were similarly studied as outpatients.

A record of the profile of residual radioactivity from the feet to the top of the head of each patient was made with a linear scanner. Recordings reflected the general distribution of radioactivity, presumably sodium-24, throughout the body. The tracings resembled the profile of the supine human body. The method permitted determination of relative amounts of remaining radioactivity and, by comparison of the tracings, permitted serial studies of the residues remaining within the body. Although the method does not yield quantitative results, the comparisons are informative. The patients followed well-recognized patterns of the postradiation syndrome, but there was some variation among the symptoms and the amounts of radiation received. For example, the patient who had the greatest exposure had the most severe symptoms and the patient who had the smallest exposure had the second most severe symptoms and hematological changes. There was also some variation in the intensity of the exposure of the intervening patients and in their clinical and laboratory examinations. The acute radiation syndrome follows a defined sequential pattern. It takes longer to develop bone marrow depression in man than in the experimental animals used in the past and also a longer time for man to recover from the bone marrow depression. One interesting sidelight was the study made on a burro experimentally exposed to a comparable amount of radiation, which yielded results similar to those observed in man.

Several biochemical studies of the effects of the acute radiation syndrome were significant. Patients treated with beta-aminoisobutyric acid (BAIBA), a newly discovered urinary acid presumed to be a product of thymine metabolism, were observed to have excretion rates that were related to the dosages received. Although further work is needed to establish the relationship, preliminary reports indicate that BAIBA may be used to measure the severity of dosage of radiation. Exposed patients showed essentially normal biochemical findings except that taurine excretion was elevated and serine was absent from the urine. The bactericidal power of serum against enteric gram-negative bacilli was not reduced in patients exposed to large amounts of whole body radiation.

The concluding paper by Brucer summarizes the clinical, hematological, and psychological effect of the acute radiation syndrome. The author has used three-dimensional drawings to illustrate plotting dose against time and severity of symptoms. This method clearly demonstrates the problems involved in the assessment of clinical and hematological findings after whole body radiation.

The book is an excellent compilation of studies of the acute radiation syndrome and should be studied by all who are interested in the field. It contains appropriate suggestions about health physics and the prevention of radiation hazards and a well-reasoned statement of the complex medical problems connected with these unfortunate accidents.

Chronic Illness in the United States. Volume III: Chronic Illness in a Rural Area. The Hunterdon Study. Reported by Ray E. Trussell, M.D., M.P.H., Chairman, School of Public Health and Administrative Medicine, Columbia University, New York, and Jack Elinson, Ph.D., Associate Professor, School of Public Health and Administrative Medicine, Columbia University. Study of prevalence of chronic illness and needs for care in rural area. Conducted by Hunterdon Medical Center, with assistance from National Opinion Research Center, and State of New Jersey Department of Health. Supported by grants from Commonwealth Fund and sponsored by Commission on Chronic Illness. Cloth. $7.50. Pp. 440. Published for Commonwealth Fund by Harvard University Press, Cambridge 38, Mass.; Oxford University Press, Amen House, Warwick Sq., London, E. C. 4, England, 1959.

This third volume in a series of four volumes is the companion work to volume 4, which presented a survey of chronic illness in a large city. The present volume, in keeping with the high standards of the other three, presents a carefully documented assessment of chronic illness in a rural area. The region selected was Hunterdon County, a prosperous area in northern New Jersey, along the Dela-

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These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

ware River. This county has 26 municipalities, 14 townships, 10 boroughs, one town, and one city. Only two of these municipalities have more than 4,000 residents. The people of this region have a strong interest in community and civic affairs.

The Hunterdon study is a report by Drs. Ray E. Trussell and Jack Elinson of the School of Public Health and Administrative Medicine, Columbia University. They were ably assisted by an adequate staff. They took the classic approach of appraising the community in general and using family interviews with multiple-screening procedures for the purpose of determining the extent of long-term illnesses in this region.

This volume has 15 chapters, 5 appendixes, and an index. Experience with previous studies was rewarding since a number of important observations were made during them. The number of the various disorders which were discovered was far in excess of earlier estimates. The survey was divided into five interrelated but successive phases: the community's survey of itself, the family interview, medical verification, clinical evaluation, and multiple screening. The results represent six months of full-scale planning and pretesting, two and one-half years of intensive survey work, and two years of analysis and reporting. The close cooperation between the doctors in the community and those who were conducting the survey is evidenced by the fact that 85% of the physicians replied to questionnaires.

The appendixes include the forms used in the survey, case reports of successful recruitment of a person for clinical evaluation who had initially refused to cooperate, code numbers and diagnoses used, the outline used by the social worker, and the diagnoses made in clinical evaluation. This book should prove an inestimable help for the staff now working on the National Health Survey. It should also prove illuminating to faculties of our medical schools and, indeed, to the student body. General practitioners, public health physicians, social workers, and leaders in the broad fields of community welfare should find here an invaluable source of information that is essential for a better understanding of the challenge of long-term illness in the rural communities of the nation.

Ciba Foundation Symposium on Carcinogenesis: Mechanisms of Action. Editors for Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., and Maeve O'Connor, B. A. Cloth. $9.50. Pp. 336, with 48 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1959.

The 29 papers presented here were given at the Ciba Foundation in 1958 just before the Seventh International Cancer Congress, which was held in London. In the first chapter, I. Hieger of London discusses the various theories of carcinogenesis, most of which are presented in [illegible] book. The relatively new theory that viruses may cause cancer is ably discussed by Jacob Furth of Boston. His theory may be summarized by the statement that we may "think of tumor-producing viruses as self-replicating nucleic acids, probably DNA" and should "distinguish sharply between two type of conceivable changes: cytogenetic and parasitic."

The immunological aspects of cancer are discussed by Green, who has been interested in this phase of research for many years. He reviews the theory that "malignant change is due to loss of factors conferring immunological identity on the cells of a tissue." It is his contention that lipoproteins are specifically involved in the immune reactions. The mechanisms of production of bladder cancer have been discussed ably by Boyland. The production of leukemia and other types of malignant tumors in mice by injection of filtrates obtained from organs of mice having leukemia, as reported first by Gross in 1951, is presented by Latarjet of Paris. One of the interesting and informative features of this volume is the discussion of the various papers. Since practically all of the authors were working in the field of carcinogenesis and were well acquainted with each other, this discussion becomes still more pertinent and valuable.

Neurology of Infancy. By Anatole Dekaban, M.D., Ph.D., Head, Section on Developmental Neurology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md. Cloth. $12. Pp. 388, with 185 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2, 1959.

The author of this welcome addition to the literature of pediatric neurology states in the preface that his two main objectives in writing this book were to describe anatomic and developmental landmarks of the maturation of the central nervous system in infancy and to outline the principles of pathology, pathogenesis, and clinical manifestations of the neurological disorders of infancy, with special emphasis on the differences between such processes in the infant and the adult. The book opens with an excellent chapter on the developmental anatomy and physiology of the nervous system during the first two years of life, with concise descriptions and photographic illustrations of the gross and microscopic anatomy of the brain and spinal cord at birth and at the four subsequent six-month intervals. Good discussions are presented of the rate of myelination, the development of cytoarchitecture, the maturation of cellular components of the nervous system, the neurophysiological development of the infant, and the average rate of acquirement of motor and intellectual skills, with tables showing normal physical measurements and indexes.

The second chapter is a valuable description of methods of examining the infant neurologically; it discusses techniques not well known even among well-trained neurologists. In the remaining chapters the reader finds discussions of birth injuries, vascular disorders, infections (including meningitis, numerous varieties of encephalomyelitis, poliomyelitis, and fungus infections), dysrhaphic states, cerebral palsy, epilepsy, mental deficiency, dysgenic states, neoplastic and granulomatous formations, metabolic and endocrine disorders, neurodegenerative diseases, and the myopathies. Extensive and well-chosen references add much to the value of each chapter. Profuse illustrations portray clinical, roentgenographic, and gross and microscopic pathological features of the neurological diseases of the infant. An adequate index gives references to subject matter and to illustrations. The binding is attractive and sturdy, befitting a book designed for use in hospital or clinic.

For the most part this is an admirable work. The initial chapter on anatomic and neurophysiological maturation is an ideal introduction to a textbook of pediatric neurology. The author rightly maintains that knowledge of normal development is necessary for any evaluation of neurological abnormality in the infant but that this field is often neglected. Disease of a portion of the brain not yet functioning can scarcely be detected; for example, one cannot speak of a defect of motor or mental skills until those skills should have been acquired. The chapter on the neurological examination of the infant is so good that it is indispensable. The section on epilepsy is refreshingly sane and fortunately avoids the over-rating of the electroencephalogram so often evident. It is precisely in connection with epilepsy in the infant that the clinical and electrographic features of the disorder depend so clearly on the degree of maturation of the brain. It is surely the neurological immaturity of the cerebrum that renders the infant so susceptible to convulsions, determines so largely the type of the seizure, and probably makes the infant so responsive to such anticonvulsant drugs as the diones and unresponsive to others. It is therefore surprising that the author scarcely notes this striking exemplification of his own major thesis. The section on metabolic and endocrine disorders is notably direct and clear. No other single discussion of these numerous and complex conditions is at once so inclusive and so succinct. Other portions of the book are similarly valuable in coverage and organization, such as the chapters on vascular disorders, encephalitis, and mental deficiency and retardation of development.

One must nevertheless note that this book has certain defects. It is by no means an encyclopedia of pediatric neurology. Many topics are discussed superficially or vaguely, for example, the chemical basis of porphyria (p. 276), the processes underlying antoimmunization and erythroblastosis fetalis (p. 277), and the myotonic states, which are described clinically but without mention of the electromyogram (p. 371). It is unfortunate that treatment is often only casually indicated without details of administration, differential criteria, or dosages. For example, in connection with intracranial aneurysms it is stated that the presence of blood in the spinal fluid indicates bleeding and that "in a proportion of patients surgical exploration preceded by an arteriogram can be attempted if facilities permit," but no explanation is given of the principles of nonsurgical management or of the tremendous decisions necessary about the optimum time for angiography or the locations and types of lesions that should be made. Again, in a rather full discussion of poliomyelitis, there is no suggestion that a vaccine for prevention is available. Tetanus is apparently not mentioned, nor is neuritis except for the neuropathy of vitamin B_1 deficiency. Certainly the neuritis of diphtheria should have been described. Scurvy is also not dealt with, though hemorrhages resulting from it may occur in the subdural space, orbit, and elsewhere with serious neurological consequences. No reference is made to the convulsive states due to deprivation of vitamin B_6.

A few errors are apparent. Hutchinson's teeth in congenital syphilis appear only in the second dentition, never during infancy (p. 127); acute syphilitic meningitis is a serious and fatal disease and does not "tend to subside even if not treated" (p. 128); and the pyramidal tracts are not involved in the Werdnig-Hoffmann type of spinal muscular atrophy. Despite these flaws the book should be of value to the young pediatrician, general practitioner, and neurologists who are unfamiliar with young patients.

Biopsy Manual. By James D. Hardy, M.D., Professor and Chairman of Department of Surgery, University of Mississippi School of Medicine, Jackson, James C. Griffin, Jr., M.D., Assistant Instructor in Surgery, University of Mississippi School of Medicine, and Jorge A. Rodriguez, M.D., *Assistant Professor of Surgical Anatomy, Department of* Surgery, University of Mississippi School of Medicine. Cloth. $6.50. Pp. 150, with 54 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

The authors of this volume describe indications, techniques, precautions, errors, and complications in connection with biopsies in general and for specific regions. They emphasize the importance of taking a sufficiently large piece of tissue or multiple pieces without crushing or tearing and furnishing of pertinent clinical information to the pathologist so that he can make studies necessary for proper diagnosis. They recognize the need in some cases for studies on fresh unfixed tissues to find bacteria, fungi, or even viruses. They also call attention to the importance, especially in office practice, of prompt fixation in a suitable fixative of the ordinary routine biopsy specimen, taken, as a rule, to determine the presence or absence of malignancy. Various fixatives and their formulas and uses are described. The addition of 10 Gm. of sodium bicarbonate to one gallon of 10% formalin, as suggested by the authors, is not to be recommended however. Many pathologists and surgeons will not agree with some of the recommendations for fixation of various tissues and serous fluids. In this phase of pathology, previous arrangements made between surgeons and local pathologists should be followed.

Later chapters contain ably illustrated orthodox information about obtaining material for pathological study from nearly every organ in the body. This information will be helpful to general practitioners, surgeons, and specialists in many fields Instruments used in various portions of the body are shown and described. The problem of the use of properly chosen anesthetics and management of any reactions to them is well presented. Fundamental surgical principles as well as technical details for the more skilled operator are discussed in detail. The subject of the use of excisional biopsy for diagnosis and cure of some lesions of the skin is ably handled. Chapters of interest to most readers should be those concerning skin, lymph nodes, breast, oral cavity, organs of the neck, rectum, prostate, bladder, cervix, and endometrium.

For those who wish information on preparing vaginal and cervical smears for cytological examination, a fairly comprehensive description and discussion of this subject is included. Techniques and indications for obtaining specimens of tissues in the thorax, abdomen, mediastinum, kidney, and adrenal gland are also described. Techniques for obtaining marrow by puncture or removal of a portion of bone and marrow should be of interest to the hematologist. A comprehensive bibliography is appended. This book should be useful as a guide in teaching medical students, interns, and resident staff members in hospital training and as a reference book for the practitioner who has had sufficient experience to warrant his use of the techniques described.

The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities. By Philip Lewin, M.D., F.A.C.S., F.I.C.S., Professor of Orthopaedic Surgery, Post-graduate Medical School of Cook County Hospital, Chicago. Fourth edition. Cloth. $14. Pp. 612, with 339 illustrations, special drawings by Harold Laufman, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School, Chicago. Lea & Febiger, Washington Sq., Philadelphia 6, 1959.

This new edition of a most reliable and comprehensive textbook has been greatly improved. The carefully outlined subject matter of the previous editions has received detailed attention so that the student, resident, and surgeon may depend on it to include the most recent details to be found in the literature on the subject. Many illustrations have been added or substituted to conform to the modern concepts of cause, diagnosis, and treatment. This book adequately covers the entire subject of the foot and ankle. The author has been careful to establish anatomic, physiological, and biomechanical basic principles on disturbances of these parts. The book covers the subjects of congenital defects and deformities; disturbances of the epiphyses of the foot and ankle; affections of muscles, tendons, fascias and bursa; injuries, including sprains, strains, fractures, and dislocations; and estimations of foot and ankle disability. These subjects are discussed from the civilian and military viewpoint. The author has brought up to date the teachings on amputation, local anesthesia, skin grafting, peripheral vascular lesions of the lower extremities, anterior poliomyelitis, and cerebral palsy, and techniques of transplanting tendons and arthrodesis, and other procedures. This book can be highly recommended as a complete textbook on the foot and ankle.

Dermatologie und Venerologie einschliesslich Berufskrankheiten dermatologischer Kosmetik und Andrologie. In fünf Bänden. Herausgegeben von Prof. Dr. Dr. h.c. H. A. Gottron, Direktor der Universitäts-Hautklinik Tübingen, und em. o.ö. Prof. Dr. Dr. h.c. W. Schönfeld. **Band III, Teil 2: Krankheiten der Hautanhangsgebilde einschliesslich Akne und Rosacea.** Bearbeitet von R. Baumann et al. Mit Namen- und Sachregister für Band III, Teil 1 und 2. Cloth. 178 marks; $42.40. Subscription price 142.40 marks; $33.90. Pp.695-1401, with 317 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

Although the title of this volume indicates that it deals with diseases of the skin appendages, including acne and rosacea, it covers a much larger territory, much of it in a masterful manner. Some of the longer chapters deal with diseases of the sudoriferous and sebaceous apparatus, hairs and nails, eruptions associated with deficiency states, metabolic and endocrine disturbances, leukemia, lymphomas, and diseases of the liver, pancreas, urogenital system, and gastrointestinal tracts. A summary of the basic histopathological, physiopathological, and biochemical features is presented in most chapters, with the etiology, clinical features, differential diagnosis, and management of the various diseases.

A successful attempt has been made to cover the literature with plentiful references to work published in European and non-European countries. As would be expected in a work of this type, few of the references are more recent than 1957. The names of the authors of pertinent work are found in the text and the detailed references are found at the end of each chapter. Perhaps too much stress is placed on fancy nomenclature such as "erythema hyperceratoticum dyspepticum supra-articulare digitorum (Csillag)." The clinical and histopathological illustrations are of superior quality. While management of the various cutaneous diseases covered in this volume is included, this book is a reference work rather than a guide for the practitioner. As such it should be highly useful for the dermatologist and nondermatologist.

QUESTIONS AND ANSWERS

DISSOLUTION OF BILIARY STONES WITH ETHER

To the Editor:—*A 70-year-old patient has had a cholecystectomy and removal of stones from the common bile duct. Two years later he had a second episode of jaundice, and after biliary calculi had been removed from the common bile duct a T-tube was put in place for irrigation of the duct. Last summer this series of events recurred and the second T-tube is still in place. Since then I have irrigated the T-tube weekly and each time have flushed out small stones. The patient suffers no discomfort except from the T-tube, which is deteriorating. I have read about the ether treatment for the dissolution of gallstones. Would this therapy be suitable for my patient?*

Sam B. McFarland, M.D., Lebanon, Tenn.

Answer.—The ether treatment (Pribram method) attains its best results in patients whose stones consist entirely or mainly of cholesterol, because the latter is soluble in ether. If the calcium content of the stone is high (as determined by roentgenogram), the ether method is of little or no help. It is better to have a catheter in the common bile duct than a T-tube, because the ether will pass through both limbs of the T-tube and cause pain and liver damage by flowing through the cephalic branch of the tube. It is helpful to administer 1/100 grain (0.6 mg.) of nitroglycerin, sublingually, at the time of etherization, for this relaxes the sphincter of Oddi and facilitates passage of small fragments of the stones. In the patient described, it might become necessary to reoperate, with performance of immediate cholangiography, if possible, and the placement of a catheter into the common bile duct for later roentgenographic study and etherization.

AUTO-UROTHERAPY

To the Editor:—*What is the efficacy of treatment, for a patient with migraine headaches, which includes injections of the patient's urine?*

Harold L. Boyer, M.D., Las Vegas, Nev.

Answer.—There is no scientific evidence which will substantiate either the rationale of this treatment or the hypothesis usually advanced by its proponents that "the antigens responsible for the headache are filtered through the glomeruli of the kidneys rather than passing from the capillaries into the tissue spaces (the usual route). By mechanically transferring the antigens to the tissue spaces by intramuscular injection of the sterile urine the allergy may be overcome."

Claims of successful treatment with auto-urotherapy can most likely be found, but it must be remembered that the patient with migraine headache often has emotional factors superimposed on the organic lesion. The use of urine as a placebo in these circumstances seems somewhat medieval in nature.

LOSS OF HAIR IN YOUNG WOMAN

To the Editor:—*A 21-year-old woman had a normal growth of hair until she was 18 years of age, at which time her hair began to fall out. Next, the hair became oily and the loss of hair increased. During the following year she became pregnant, and in the fourth month of pregnancy her hair stopped falling out, new hair began to grow, and the oiliness decreased. One month after delivery of the baby, her hair again began to fall out and became oilier. During the patient's second pregnancy, at the age of 21 years, the process of hair restoration, followed by thinning after delivery, repeated itself. The hair distribution on the rest of her body is normal and has not been affected. Her menses have been normal. Please comment on this patient's problem.* *M.D., New York.*

Answer.—The history presented by the patient is not unusual. The patient has seborrhea oleosa which is described in Behrman's chapter on seborrheic diatheses (The Scalp in Health and Disease, St. Louis, C. V. Mosby Company, 1952, pp. 220-234). The excessive amount of oily secretion bathes the hair and scalp, thus causing a glossy appearance, and, in some patients, is associated with the type of progressive loss of hair referred to as "female-patterned" alopecia. The oiliness and the loss of hair often decrease during pregnancy because of the resultant hormonal changes.

The mechanisms of these clinical observations are not specifically understood, although it is obvious that various hormonal factors are involved. In general, it has been assumed that androgenic hormones increase both sebaceous gland excretion and loss of scalp hair, while estrogenic hormones have the opposite effect. Unfortunately, such assumptions are not confirmed sufficiently to warrant specific

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

estrogen therapy, unless thorough endocrine studies indicate its value in a patient. The endocrine balance of each patient should be thoroughly studied, and therapy should be specifically related to the findings obtained. In some patients the administration of estrogens and di-iodothyronine have been beneficial. Local measures, such as use of antiseborrheic shampoos and lotions, may be of some help.

NODULES IN THE TENDO ACHILLIS

To the Editor:—*A 64-year-old dentist has painful nodules in the tendo achillis just above the ankle joint, which bother him when he walks. Results of diagnostic tests on blood and urine specimens have been negative, and a roentgenographic film showed the nodules to be soft tissue swellings without calcification. The only treatment given has been injection of hydrocortisone into the nodules, with resultant temporary relief from pain. What should be done to obtain a definite diagnosis, and what treatment can be recommended?*

F. K. Hurt, M.D., Jacksonville, Fla.

Answer.—The type of nodules described usually are of arthritic origin and are likely to occur in patients with gouty arthritis. A finding of a normal blood level of uric acid in a single, or even several, specimens does not rule out this condition. The nodules due to gout have a characteristic microscopic appearance. The only treatment for the nodules is excision, and, unless the patient is treated for his general systemic disease, the nodules are likely to appear elsewhere and may recur in or near their original site.

BREAST CANCER AND OOPHORECTOMY

To the Editor:—*Should an oophorectomy be performed as a prophylactic measure in all patients with cancer of the breast, or should it be used only for patients who have metastatic lesions?*

Paul B. Shuey, M.D., Long Island City, N. Y.

Answer.—A categorical answer is not possible because knowledge of estrogen-dependent or non-estrogen-dependent breast cancers is incomplete. There is no accurate way to determine the effect estrogen may have on a specific malignant lesion, but an estimate of estrogen dependence can be made from the histological picture of the breast tumor. A well-differentiated breast carcinoma is presumed to have estrogen dependence whereas the undifferentiated carcinoma is considered to be non-estrogen-dependent. The premenopausal patient with breast cancer should be considered a candidate for oophorectomy, which should be performed at the time of radical mastectomy. The general consensus, however, is that oophorectomy in the premenopausal patient is desirable in all cases.

Although the premenopausal patient is a candidate for oophorectomy, each patient must be appraised by the attending surgeon, with serious consideration of the total patient problem before he decides whether or not that patient should undergo this operation. Oophorectomy is not categorically indicated for all patients with metastatic breast cancer but definitely should be considered, especially if the patient is still menstruating. Regression of metastatic lesions in soft tissues compared to that in bone after oophorectomy depends on several factors. The lesions with the highest incidence of regression are those located in skin, subcutaneous tissue, and lymph nodes, while regression of metastasis in bone is less marked.

In the postmenopausal patient adrenalectomy must be considered in addition to oophorectomy, since the ovaries may still have functioning stroma. The type of soft tissue involved, the age of the patient, the other sources of estrogen, such as the adrenals, are the factors that must be considered in endocrine palliative therapy for metastatic breast cancer.

IDIOPATHIC EDEMA

To the Editor:—*A 29-year-old woman has had three normal pregnancies during which she had no excessive weight gain, albuminuria, or glucosuria. Three weeks after the termination of her second pregnancy she developed edema of both legs, more severely in the right one. A complete physical examination did not indicate any abnormalities. The edema lasted for three weeks, then disappeared spontaneously, and reappeared two years later. Edema, more severe than before, occurred about 10 days after the delivery of her third child; it was present for one month and again subsided spontaneously. No cause for the edema has been found. She has had no other signs or symptoms. Can you supply any suggestions as to the possible cause of the edema in this patient and the type of further investigative study to be done?*

R. F. DeWitt, M.D., Plymouth, N. H.

Answer.—Although there is no history of pain, tenderness in the legs, or fever, deep venous thrombosis is the most likely diagnosis. A careful examination, including the Trendelenburg test, of the patient's leg veins might disclose incompetent valves of the deep veins which result from deep venous thrombosis. Absence of this finding does not exclude the diagnosis. The exact distribution of the edema can be used to establish the location of thrombi which may be in the femoral or iliac veins or in the vena cava. Lymphatic obstruction can cause a rapid accumulation of edema fluid but such edema is not likely to subside spontaneously. Intravenous urography and barium enema examination are useful in the exclusion of lymphatic obstruction of the pelvic region. Edema due to heart or kidney disease is not a factor, since the patient has no signs or symptoms of such illnesses.

If the patient desires another child, another pregnancy would not be contraindicated. If the edema recurs, concomitant heparin and hydrochlorothiazide therapy should be given, even though there is no other evidence of venous thrombosis.

LOSS OF HEARING FROM GUN NOISE

To the Editor:—*Will the loss of hearing due to loud noises (firing of rifle and/or pistol) be temporary or permanent? Should one discontinue shooting or can ear plugs be used to prevent loss of hearing from loud noises?* *M.D., Nevada.*

Answer.—If the loss of hearing caused by firing of guns has persisted longer than 7 to 10 days, it will be permanent, but frequently it will last only a few days. Once the condition has become permanent, there is no treatment. If the loss has occurred over a short period and from firing only a few rounds of ammunition, the patient should discontinue shooting. If it has occurred over a long period (10 to 15 years), there is no reason to discontinue shooting. It is best to wear ear plugs while shooting, because they do prevent injury due to loud noises.

UNTOWARD REACTIONS TO LOCAL ANESTHETICS

To the Editor:—*Can intradermal or conjunctival tests be used to determine a patient's sensitivity to local anesthetics? If the patient does have such a sensitivity, is it possible to desensitize him?* *M.D., Alabama.*

Answer.—Although local anesthetic agents may produce an abnormal systemic reaction in a patient, it is doubtful that any anesthetics commonly used could cause true tissue sensitivity that would be prevented by graduated doses of these agents. Allergic manifestations of this nature usually depend on the presence of a protein which is involved in the antigen-antibody reaction.

Reactions to local anesthetic agents administered to the patient prior to dental repair consist of palpitation, dizziness, or fainting. These can be caused by epinephrine or other vasoconstrictors in the solution, or by emotional instability of the patient. Any local tissue swelling which may occur has been attributed to histamine release and can be prevented by administration of an antihistaminic drug. Localized tissue swelling also can be the result of increased reaction by the patient's tissue to trauma.

The future management of a patient who has had one episode of local tissue swelling and may need further dentistry would include a history of the agents used prior to the reactions and knowledge of whether or not vasopressor drugs had been included in the solutions. Since anesthetic agents of distinctly different structure and composition are available, it is possible to use one not related to the one previously administered. Although the value of skin testing is questionable, it should be performed with the agent to be used. Use of vasopressor drugs should be avoided, and it might be wise to give the patient an antihistamine prior to injection of the anesthetic. Should skin tests indicate a reaction, the local nerve block technique should be avoided and a general anesthetic, such as nitrous oxide, given.

GLUCAGON

To the Editor:—*Is the treatment of a patient with insulin hypoglycemia by intramuscular administration of crystalline glucagon (hyperglycemic-glycogenolytic factor) safe and practical? Where can glucagon be obtained? Elrick and associates wrote on this topic (Glucagon Treatment of Insulin Reactions,* New England J. Med. 258:*476 [March 6] 1958).*

H. M. Jardine, M.D., West Branch, Mich.

Answer.—Management of insulin hypoglycemia by glucagon is entirely safe. The levels of blood sugar obtained from the blood of a patient treated with glucagon are in the normal range or somewhat higher but never excessive. Mild or moderately severe insulin reactions can and should be treated by the patient through ingestion of sweetened food or drink. Severe reactions usually are managed by his family or a physician. It is doubtful that an ordinary family would have a member with sufficient knowledge of technique to give the injection of glucagon. If given by the physician, it does provide a safe and effective means of treatment, and, since intravenous injection is not necessary, it has an advantage over the intravenous administration of dextrose. Glucagon is not commercially available.

ARGYRIA FROM SILVER NITRATE CAUTERIZATION

To the Editor:—*Could argyria result from the repeated application of silver nitrate in cauterization of the edges of the healing tissue of a patient on whom a pilonidal cyst excision has been performed? The applications are done 6 to 10 times weekly.*

Lucian J. Fronduti, M.D., New Kensington, Pa.

Answer.—There appears to be no record of argyria occurring in a patient from the use of silver nitrate on a pilonidal surface wound. The granulation tissue should be cut away so that a lesser amount of silver nitrate needs to be used, and the physician should be aware of the early symptoms of argyria. Argyria is not likely to be caused by the technique described, but there is a considerable variation in patient tolerance to the heavy metals.

TUBERCULIN SKIN TEST SOLUTION

To THE EDITOR:—*Is there a tuberculin skin test which is packaged in amounts of one to three tests, or is there a package providing solutions of old tuberculin or purified protein derivative (PPD) which, after mixing, will remain stable for more than a few days? The average physician in general practice may perform only a few tuberculin skin tests per month, and a large part of the materials contained in available packages must be discarded.* *M.D., Maryland.*

ANSWER.—A check on the availability of a one-test vial of tuberculin (PPD) did not disclose any company that markets this product in this size. The customary sizes are 10-test and 100-test packages. To prevent wastage of a portion of the 10-test vial, the physician should schedule a sufficient number of patients for tuberculin testing within a three-day or four-day period, thus making more complete use of each vial.

PREGNANCY AND QUININE TONIC WATER

To THE EDITOR:—*Several patients have inquired about the drinking of quinine water during pregnancy. How much quinine would have to be consumed by a pregnant woman to be toxic to the fetus?* *M.D., Illinois.*

ANSWER.—Deafness in a newborn child has been attributed to administration of therapeutic quantities of quinine to the mother during pregnancy, and for this reason use of the drug has been abandoned for the induction of labor. Apparently no toxic effects have occurred in the fetus from maternal doses below 600 mg. daily. The quantity of quinine hydrochloride in a 10-oz. bottle of "tonic water" is about 25 mg. An expectant mother would have to consume more than 20 bottles of quinine water daily before toxicity might be seriously considered.

PIGMENTED SPOTS ON THE FACE

To THE EDITOR:—*A 34-year-old woman has numerous so-called "liver spots" on her forehead and both cheeks. She is married to an Air Force officer and has lived in various regions of the United States and in foreign countries. She has no children and is not pregnant. What type of dermatosis is this?* *M.D., Alabama.*

ANSWER.—Liver spots usually are described as circumscribed, irregular areas of macular pigmentation on the exposed areas of the face; they occur frequently in women. Other names for this pigmentation are melasma and chloasma. The pathogenesis of these lesions is unknown. In northern latitudes the pigmentation frequently becomes almost imperceptible during the winter months and is, therefore, not a new melanin formation but a seasonal darkening of pigment related to solar exposure. This darkening of pigment can be prevented by application of a chemical sun filter which blocks the long-wave ultraviolet rays of sunlight.

PSEUDOCYST OF THE PANCREAS

To THE EDITOR:—*A 28-year-old man, injured in an automobile accident, received an injury which lacerated the superior portion of the pancreas but did not involve the major duct. The capsule of the pancreas was repaired, and a drain was placed through the abdominal wall which extended down to the injured site. Copious drainage occurred on the 3rd but stopped by the 10th postoperative day. The patient has had no pancreatic symptoms since recovery from his injuries. What is the possibility that a pancreatic pseudocyst might develop?*

M.D., South Carolina.

ANSWER.—Assuming that results of all the usual tests for pancreatic dysfunction and of other examinations of this patient are normal, he may be considered cured. The published records of patients with pancreatic lacerations who have not developed pseudocysts are inadequate for estimation of the incidence of cyst formation. From the reports of pseudocysts occurring in patients with a history of injury one might set the incidence at about 2%.

NEUROFIBROMATOSIS AND CATARACTS

To THE EDITOR:—*A woman has neurofibromatosis, with lesions located everywhere on her body. She also has a cataract of the right eye, degeneration of the retina of the left eye, and myopic vision (20/200). Several ophthalmologists have hesitated to remove the cataract because partial degeneration of the retina in the right eye has occurred, so that she might not be benefited by this operation. The patient's present treatment includes injections of liver, vitamin* B_{12}*, and vitamin A. Her loss of vision has increased only slightly during the past two years. Are there any other medicaments which would improve either the retinal condition or the neurofibromatosis? Do these conditions usually occur concurrently?*

E. Milton Staub, M.D., Westfield, N. J.

ANSWER.—Neurofibromatosis may involve any structure of the eye, but this patient's cataract appears to be unrelated to the disease. The occurrence of retinal degeneration, if not associated with tumor, is also incidental. There are no medical remedies which are of benefit to the patient with either of these conditions.

WASHINGTON NEWS

Administration Considers New Health Bill . .
Water Pollution Bill . .
Health Budget Rapped . .

SENATE SUBCOMMITTEE RECOMMENDS FORAND-TYPE PROGRAM

Arthur S. Flemming, Secretary of Health, Education, and Welfare, told a news conference he "hopes" to send to Congress within 60 days a measure aimed at meeting some of the health needs of elderly persons.

He declared his department is working on three approaches to provide catastrophic health insurance for the aged, through (1) the social security system; (2) Public Assistance Program grants; or (3) some form of supplementing voluntary private insurance. He emphasized that no conclusion had been reached yet within the administration on which type of program to support. His remarks followed a similar statement made by President Eisenhower at his weekly meeting with reporters.

In another important development here, the special Senate labor subcommittee on aging issued its long-awaited report, which endorsed a sweeping program of health care for the aged through the social security system. The Democratic majority of the subcommittee, headed by Sen. Pat McNamara (D. Mich.), concluded that "The no. 1 problem of America's senior citizens is how to meet the cost of health care at a time when income is lowest and potential or actual disability at its highest."

In reply, Dr. Louis M. Orr, President of the American Medical Association, declared that the subcommittee was "politically inspired." He pointed out that at seven subcommittee hearings throughout the country last fall "observers heard little support expressed by the older citizens who attended the hearings for government medicine financed by additional taxes and administered through social security."

The two Republican members of the subcommittee, Senate GOP Leader Everett M. Dirksen (Ill.) and Sen. Barry Goldwater (Ariz.), also took issue with the Democrats' recommendations. In a dissenting report, they said "It is possible for elderly people to secure private insurance to provide hospitalization and surgical benefits without any intervention by public authorities."

The two senators pointed out that the broad programs proposed by the Democrats would add billions of dollars to the cost of the federal government and thereby promote inflation, which is one of the major problems of old persons living on fixed incomes. "The problems of older Americans are basically no different from those of other citizens," the minority report said. "Their principal concern is to see the value of their savings protected by sound monetary and fiscal policies on the part of the federal government."

In addition to a Forand-type health recommendation, the subcommittee called for a hike in cash benefits for social security beneficiaries; federal subsidies for nursing homes "which meet the minimum standards for medical and restorative services"; establishment of a U. S. Office of the Aging; a 100-million-dollar annual program of housing for the elderly; and elimination of job discrimination against older persons.

Protesting the scope of the recommendations, senators Dirksen and Goldwater said they would "add to the tax burdens of everyone, raise prices, and ultimately depreciate the purchasing power of the savings of those who are no longer able to work."

"As with so many other studies, the majority's report raises false hopes that the federal government will be able to solve problems which are not susceptible to solutions by congressional enactments," said the Republicans.

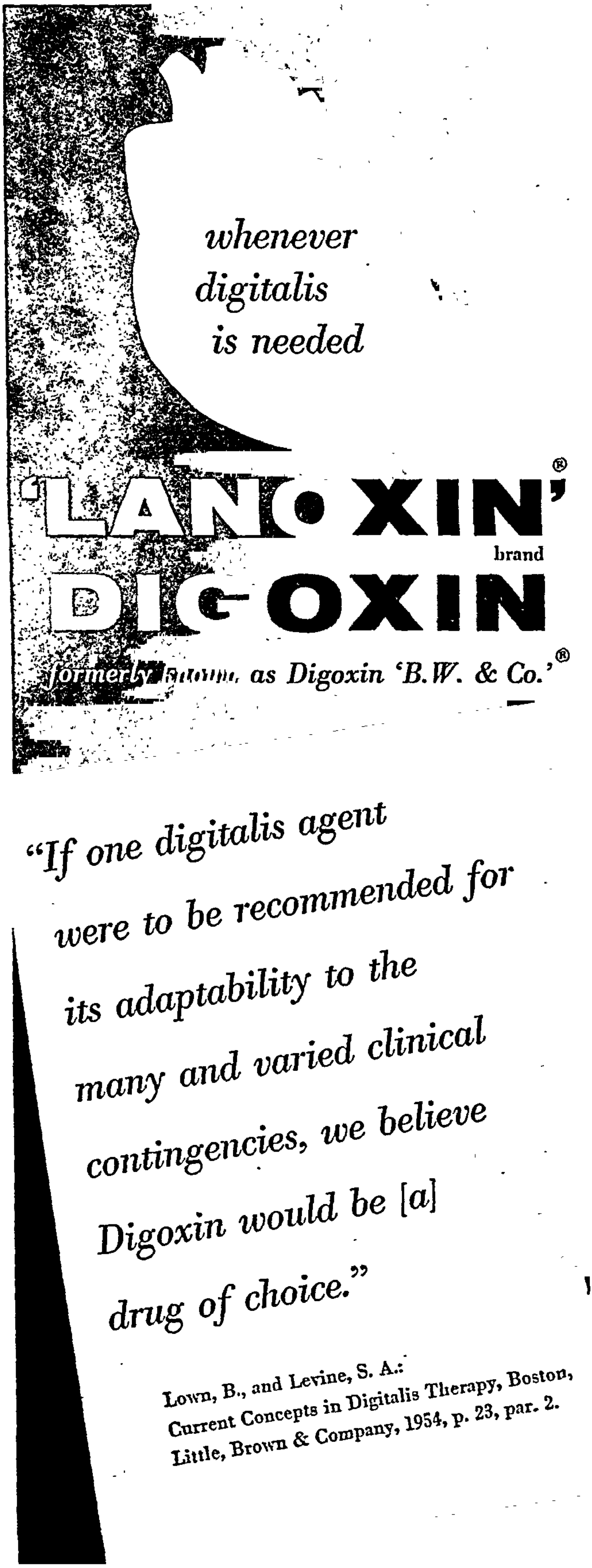
In addition to Senator McNamara, the other Democratic members of the subcommittee were senators John Kennedy (Mass.), Jennings Randolph (W. Va.), and Joseph Clark (Pa.). Senator Kennedy, leading candidate for the Democratic presidential nomination, has introduced a bill that would be broader in most respects than the controversial Forand proposal.

HEW Secretary Flemming at his news conference said he wanted to "underline that the position of the administration still is in opposition to the Forand bill" that would finance partial health care for the aged through higher Social Security taxes. He gave a flat "no" in reply to a question whether the administration had reached a conclusion that the only way to deal with the problem is through the social security system. Vice-president Richard Nixon, said Flemming, was "very obviously participating" in administration discussions on the matter.

The American people, as well as the administration, he said, have "deep-seated concern" about the problem of catastrophic illnesses of the aged. He said he doubted that voluntary insurance, alone, regardless of its progress in that field, will ever be able to come up with a complete solution.

Meanwhile, the House Ways and Means Committee was scheduled to start sessions in late March or April on various proposals to change the social security laws that might include health care meas-

(Continued on next page)



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Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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ures. What action, if any, the Committee takes will be of extreme importance, since it must originate all social security legislation.

WATER POLLUTION CONTROL BILL APPROVED

The House approved legislation to allow a 90-million-dollar annual program of federal grants to help localities build sewage disposal plants and take other steps to combat water pollution. The measure went far beyond the administration's recommendation that the program be limited to federal spending of 20 million dollars a year, with the communities shouldering more of the burden.

Under the bill, passed by voice vote, individual projects could receive up to $450,000 of federal money, compared with the present limit of $250,000

The measure cleared by the House was a compromise between a broader House bill and a more limited Senate measure acted on last year.

The federal government was armed by Congress with stiff powers a few years ago to order localities to clean up pollution on waterways involving interstate commerce, and the Department of Health, Education, and Welfare has already handed down several decisions compelling municipalities to move against pollution.

LAWMAKER CRITICIZES HEALTH BUDGET CUTS

Sen. Lister Hill (D., Ala.), chairman of the Senate appropriations subcommittee on health, promised to try to restore the budget reductions sought in some programs by the administration. He especially criticized the 60-million-dollar reduction sought in the Hill-Burton program of aid for hospital construction, declaring that "President Eisenhower persists in proposing crippling budgets for this vital program in the face of overwhelming evidence that all hospital construction is insufficient to replace the hospital beds lost through obsolescence and those needed to meet the population increases."

Although some health programs were decreased in the budget, the over-all spending in this field by the government next fiscal year would be 100 million dollars more than this year under the President's budget.

MISCELLANY

The U. S. Public Health Service said heart disease, strokes, cancer, and accidents accounted for 71% of all deaths in 1958. Recorded were 1,647,886 deaths that year, a rate of 9.5 per 1,000 population, compared with 9.6 in 1957. The 1958 toll included 637,246 deaths from heart disease, 190,758 from strokes and other vascular lesions, 254,426 from cancer, 36,981 deaths from automobile accidents, and 53,523 from other kinds of accidents.

PHS Surgeon General Leroy E. Burney has invited a delegation of 13 Russian scientists to this country in May for joint scientific meetings in the fields of cancer and heart disease. Dr. Burney also proposed that missions of scientists from the United States to the Soviet Union begin next October with a delegation in the field of maternal and child care.

President Eisenhower asked Congress for an extra $332,000 this year for the Food and Drug Administration to buy equipment for an expanded study of radioactivity in food.

Rep. John Fogarty (D., R. I.,), Chairman of a House appropriations subcommittee on health expenditures, introduced a bill for a 2-million-dollar annual program of scholarships for medical students. Eight thousand scholarships of up to $2,500 would be provided under the proposed 10-year program.

In a letter to Chief Justice Robert G. Simmons of the Supreme Court of Nebraska, who has suffered a heart attack, President Eisenhower had this to say: "From my own experience with a coronary, I bid you be of good cheer awaiting complete recovery. As one who had a similar experience, I can only suggest that you faithfully follow the doctor's orders, tedious as they may make the next weeks or months; but I am certain that you will without too much delay be able to resume your normal routine."

Many drug addicts are switching to cough medicines as a cheap and easily obtainable substitute for narcotics, Narcotics Commissioner Harry J. Anslinger reported. The cough syrups contain dihydrocodeinone, an opium derivative, and can be purchased across the counter at drug stores, he said.

The Federal Trade Commission said the nation's cigarette manufacturers have decided to end health claims in cigarette advertising, a move labeled as "a landmark example of industry-government cooperation in solving a pressing problem" by FTC Chairman Earl W. Kintner.

The Air Line Pilots Association brought suit in federal district court in New York seeking a temporary injunction against a Federal Aviation Agency decision to require retirement of commercial air line pilots at the age of 60 years.

The Agriculture Department ordered meat inspectors to bear down on enforcement of a regulation aimed at keeping residues of stilbestrol out of meat. The Department and the Food and Drug Administration had received complaints about violations of the rule which calls for a time interval before slaughter after the animals have been fed grain containing stilbestrol, a product that has caused cancer when fed in large quantities to test animals.

The State Department set up an interdepartmental committee on international health policy, headed by HEW Secretary Arthur S. Flemming. The committee "will function as a regular mechanism for advising the Secretary of State as to objectives, establishing long-range goals, and planning programs in the field of international health," said Flemming.

The National Institutes of Health awarded 20 grants, totaling $733,143, to support the training of research scientists in basic medical and health-related sciences. These awards, part of an NIH effort to stimulate more research training in the scientific fields basic to medicine and public health, were made to 20 institutions and universities in 16 states to provide support for the training of graduate students and postdoctoral trainees in a number of basic sciences, including embryology and development, biochemistry, physiology, microbiology, medical genetics, anatomic sciences, pharmacology, basic multi-disciplinary studies, and cell biology.

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MEETINGS

AMERICAN MEDICAL ASSOCIATION: *Dr. F. J. L. Blasingame*, 535 North Dearborn St., Chicago 10, Executive Vice-President.
1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 2.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-Dec. 1.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 25-30.

AMERICAN

1960

February

Alaska State Medical Association, Anchorage, Feb. 18-20. Dr. George Hale, 501 "L" Street, Anchorage, Alaska, Chairman.

American College of Allergists, Inc., Americana Hotel, Bal Harbour, Miami Beach, Fla., Feb. 28-Mar. 5. Mr. Eloi Bauers, 2160 Rand Tower, Minneapolis 2, Executive Vice-President.

American College of Surgeons, North Carolina Chapter, Hotel Barringer, Charlotte, N. C., Feb. 26-27. For information write Dr. Alexander Webb Jr., 201 Bryan Bldg., Cameron Village, Raleigh, N. C.

American College of Surgeons, Sectional Meeting for Surgeons and Nurses, Statler Hilton, Boston, Feb. 29-Mar. 3. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Orthopsychiatric Association, Inc., Sherman Hotel, Chicago, Feb. 25-27. Marion F. Langer, Ph.D., 1790 Broadway, New York 19, Executive Secretary.

California Medical Association, Ambassador Hotel, Los Angeles, Feb. 21-24. Mr. John Hunton, 450 Sutter St., San Francisco 8, Executive Secretary.

Central Surgical Association, Drake Hotel, Chicago, Feb. 18-20. Dr. Angus D. McLachlin, Victoria Hospital, London, Ont., Canada, Secretary.

Symposium on Fundamental Cancer Research (14th), University of Texas, Houston, Feb. 25-27. For information write: University of Texas M. D. Anderson Hospital & Tumor Institute, Houston 25, Texas.

March

American Broncho-Esophagological Association, Deauville Hotel, Miami Beach, Fla., Mar. 15-16. Dr. F. Johnson Putney, 1712 Locust St., Philadelphia 3, Secretary.

American Academy of Forensic Sciences, Drake Hotel, Chicago, Mar. 3-5. Dr. W. J. R. Camp, 1853 W. Polk St., Chicago 12, Secretary-Treasurer.

American Academy of General Practice, *Philadelphia*, Mar. 18-24. Mr. Mac F. Cahal, Volker Blvd., at Brookside, Kansas City 12, Mo., Executive Director.

American Association for the History of Medicine, Inc., Charleston, S. C., Mar. 24-26. John B. Blake, Ph.D., c/o Smithsonian Institution, Washington 25, D. C., Secretary.

American College of Surgeons, Sectional Meeting, The Broadmoor, Colorado Springs, Colo., Mar. 21-23. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Sheraton-Portland Hotel, Portland, Ore., Mar. 28-30. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Gastroenterological Association, Roosevelt Hotel, New Orleans, Mar. 31-Apr. 2. Dr. Wade Volwiler, Dept. of Med., Univ. of Washington, Seattle, Secretary.

American Gastroscopic Society, Roosevelt Hotel, New Orleans, Mar. 30. Dr. Arthur M. Olsen, Mayo Clinic, Rochester, Minn., Secretary-Treasurer.

American Laryngological Association, Deauville Hotel, Miami Beach, Fla., Mar. 18-19. Dr. Lyman Richards, Massachusetts Institute of Technology, Cambridge 39, Mass., Secretary.

American Laryngological, Rhinological and Otological Society, Inc., Deauville Hotel, Miami Beach, Fla., Mar. 15-17. Dr. C. Stewart Nash, 708 Medical Arts Bldg., Rochester 7, N. Y., Secretary.

American Otological Society, Deauville Hotel, Miami Beach, Fla., Mar. 13-14. Dr. Lawrence R. Boies, University Hospital, Minneapolis 14, Minn., Executive Secretary-Treasurer.

American Otorhinologic Society for Plastic Surgery, Inc., Deauville Hotel, Miami Beach, Fla., Mar. 6-13. Dr. Joseph G. Gilbert, 75 Barberry Lane, Roslyn Heights, N. Y., Secretary.

American Psychosomatic Society, Sheraton-Mount Royal Hotel, Montreal, Mar. 26-27. Miss Joan K. Erpf, 265 Nassau Rd., Roosevelt, N. Y., Executive Assistant.

American Radium Society, Caribe Hilton Hotel, San Juan, Puerto Rico, Mar. 17-19. Dr. Robert L. Brown, Robert Winship Clinic, Emory University, Atlanta 22, Ga., Secretary.

Association of Clinical Scientists, DeWitt Clinton Hotel, Albany, N. Y., March 3-5. Dr. Robert P. MacFate, 54 W. Hubbard St., Chicago 10, Secretary.

Intermountain Pediatric Society, Stardust Hotel, Las Vegas, Nev., Mar. 28-29. Dr. Joseph R. Newton, 2000 S. 9th East, Salt Lake City, Utah, Publicity Chairman.

Missouri State Medical Association, Sheraton-Jefferson Hotel, St. Louis, Mar. 13-16. Mr. T. R. O'Brien, 634 N. Grand Blvd., St. Louis 3, Executive Secretary.

National Health Council, National Health Forum, Miami, Fla., Mar. 13-18. Mr. Philip E. Ryan, 1790 Broadway, New York 19, Executive Director.

National Multiple Sclerosis Society, New York City, Mar. 8. Mr. Donald Vail, 257 Fourth Ave., New York 10, Secretary.

Neurosurgical Society of America, Del Monte Lodge, Calif., Mar. 30-Apr. 2. Dr. Raymond K. Thompson, 803 Cathedral St., Baltimore 1, Secretary.

New Orleans Graduate Medical Assembly, Roosevelt Hotel, New Orleans, Mar. 7-10. Miss Irma B. Sherwood, 1430 Tulane Ave., New Orleans 12, Executive Secretary.

Southeastern Surgical Congress, Roosevelt Hotel, New Orleans, Mar. 21-24. Dr. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga., Executive Secretary.

Southwestern Society for Nuclear Medicine, Menger Hotel, San Antonio, Texas, Mar. 26-27. Dr. N. T. Werthessen, Southwest Foundation for Research and Education, R. R. 4, Box 86, San Antonio 7, Texas, Program Chairman.

Southwestern Surgical Congress, Riviera Hotel, Las Vegas, Nev., Mar. 28-31. Miss Mary O'Leary, 1213 Medical Arts Bldg., Oklahoma City, Okla., Executive Secretary.

April

Alabama, Medical Association of the State of, Admiral Semmes Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery 4, Executive Secretary.

American Academy of Neurology, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

American Association for the Advancement of Science, Section on Medical Sciences, Vanderbilt University, Apr. 18-19. Dr. George R. Meneely, Vanderbilt University School of Medicine, Nashville 5, Tenn., Chairman.

American Association of Anatomists, Statler-Hilton, New York City, Apr. 11-16. Dr. Louis B. Flexner, Dept. of Anatomy, School of Medicine, Univ. of Pa., Philadelphia 4, Secretary-Treasurer.

American Association of Immunologists, Chicago, Apr. 11-15. Dr. Calderon Howe, Columbia Univ. College of Physicians and Surgeons, New York 22, Secretary-Treasurer.

American Association of Pathologists and Bacteriologists, Hotel Peabody, Memphis, Tenn., Apr. 28-30. Dr. Russell L. Holman, Dept. of Pathology, L. S. U. School of Medicine, New Orleans, La., Secretary.

American Association of Railway Surgeons, Drake Hotel, Chicago, Apr. 7-9. Mr. Chester C. Guy, 5800 Stony Island Ave., Chicago 37, Executive Secretary.

American College Health Association, Toronto, Canada, Apr. 27-30. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary Treasurer.

American College of Obstetricians and Gynecologists, Netherland Hilton Hotel, Cincinnati, Apr. 2-6. Mr. Donald F. Richardson, 79 W. Monroe St., Chicago 3, Executive Secretary.

American College of Physicians, Mark Hopkins & Fairmont, San Francisco, Apr. 4-9. Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Executive Secretary.

American College of Surgeons, Sectional Meeting, Hotel Leamington, Minneapolis, Apr. 11-13. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Kahler Hotel, Rochester, Minn., Apr. 14. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, West Virginia Chapter, The Greenbrier, White Sulphur Springs, W. Va., Apr. 1-2. Dr. Ray E. Burger, Grace Hospital, Welch, W. Va., Vice-President.

American Dermatological Association, Inc., Boca Raton Hotel, Boca Raton, Fla., Apr. 8-12. Dr. Wiley M. Sams, 308 Ingraham Bldg., Miami 32, Fla., Secretary.

American Physiological Society, Chicago, Apr. 11-15. Ray G. Daggs, D.Sc., 9650 Wisconsin Ave., Washington 14, D. C., Executive Secretary.

American Proctologic Society, Shamrock Hilton Hotel, Houston, Texas, Apr. 25-27. Dr. Norman D. Nigro, 10 Peterboro, Detroit 1, Secretary.

American Public Health Association, Southern Branch, Memphis, Tenn., Apr. 13-15. Dr. L. M. Graves, Shelby County Health Department, Memphis, Tenn., Chairman, Local Arrangements Committee.

American Society for Artificial Internal Organs, Pick-Congress Hotel, Chicago, Apr. 10-11. Dr. Charles K. Kirby, 3400 Spruce St., Philadelphia 4.

American Society of Biological Chemists, Inc., Chicago, Apr. 11-16. Dr. Frank W. Putnam, Dept. of Biochemistry, Univ. of Florida, Gainesville, Secretary.

American Society for Experimental Pathology, Pick Congress Hotel, Chicago, Apr. 11-15. Dr. J. F. A. McManus, Univ. of Alabama Med. Center, *Birmingham*, Ala., Executive Secretary.

American Society of Facial Plastic Surgery, Hotel Elysee, New York City, Apr. 6. Dr. Samuel M. Bloom, 123 E. 83d St., New York 28, Secretary.

American Society of Internal Medicine, Sheraton-Palace Hotel, San Francisco, Apr. 1-3. Mr. Robert L. Richards, 350 Post St., San Francisco 8, Executive Director.

American Society for Pharmacology and Experimental Therapeutics, Inc., Chicago, Apr. Dr. Karl H. Beyer Jr., Merck Sharp and Dohme Research Labs., West Point, Pa., Secretary.

American Society for the Study of Sterility, Sheraton-Gibson Hotel, Cincinnati, Apr. 1-3. Dr. Herbert H. Thomas, 920 S. 19th St., Birmingham 5, Ala., Executive Secretary.

American Surgical Association, The Greenbrier, White Sulphur Springs, W. Va., Apr. 3-6. Dr. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Secretary.

Andrew, John A., Clinical Society, Tuskegee Institute, Alabama, Apr. 24-29. Dr. Eugene H. Dibble, Memorial Hospital, Tuskegee Institute, Ala., Secretary.

Arkansas Medical Society, Pine Bluff, Apr. 18-20. Mr. Paul C. Schaefer, 218 Kelley Bldg., Fort Smith, Ark., Executive Secretary.

Connecticut State Medical Society, Hamden High School, Hamden, Apr. 26-28. Dr. William R. Richards, 160 St. Ronan St., New Haven, Conn., Secretary.

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CURRENT STATUS OF ANTI-INFECTIVE THERAPY IN UROLOGY

Russell D. Herrold, M.D.
and
Nick Karabatsos, M.S., Chicago

In treating acute infections of the urinary tract, a sulfonamide drug is recommended as the first choice; if the program here outlined fails, the reason is likely to be either specific bacterial resistance or the presence of structural abnormalities. In treating chronic infections broad-spectrum antibiotics are suggested. The authors review previously published observations on 75 patients treated with kanamycin. The original organism was eradicated in about 60% of this group, but other organisms emerged after or even before the treatment was ended in about 30%. The experience of the authors indicated that underlying urologic abnormalities should be searched for, that sensitivity tests are of value in choosing the antibiotic best suited to the infecting organism, and that the possible development of resistance to the antibiotic on the part of the organism must be kept in mind.

ACUTE uncomplicated infections of the urinary tract are usually caused by bacilli. We believe that the drug of first choice is a sulfonamide, if the patient is not sensitive. It should be given in maximum dosage for at least five days and in lower dosage for an additional five days. If this therapeutic regimen fails to cure the infection, a complete urologic examination is indicated. Occasionally the lack of response is due to bacterial resistance; this is usually indicated by no subjective or objective improvement occurring in the first 48 hours of therapy. The chief current problem is the management of chronic infections without associated uropathy or with nonremediable uropathy.

In urinary infections the infecting organisms can be identified most accurately by cultures, since in this way the genus can be identified and sensitivity tests done, if indicated. If cultures are not available, gram staining of the urinary sediment, which will establish whether the infection is bacillary, "coccic," or mixed, should be done. A wet cover slip preparation is a simple method of evaluating the degree of pyuria and hematuria. Also, bacilli may frequently be identified microscopically under the high-power field, especially in samples from patients with acute infections.

The results of the disk method of sensitivity testing are more likely to correlate in vitro and in vivo if the primary inoculations are made from the patient's urine or prostatic secretion. There is usually enough growth so that it is seldom necessary to make subcultures into broth before making sensitivity tests. We believe that sensitivity readings are

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From the departments of surgery (urology) and bacteriology, College of Medicine, University of Illinois.
Read before the Section on Urology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

most important when the zones of inhibition of growth show completely resistant or highly sensitive reactions to the drug. Intermediate readings between these two areas are of some importance only when two drugs are to be given in combination.

Our observations on the newest broad-spectrum antibiotic, kanamycin (Kantrex), are based on the treatment of 75 patients,[1] predominantly adult, with chronic urinary tract infections. These patients had pretreatment cultures, and adequate follow-up studies were made in all but 11 cases. All patients had had a complete urologic examination prior to therapy. Kanamycin should not be given to patients with infections due to enterococci such as Streptococcus faecalis. Frequently such organisms could be isolated during therapy or immediately thereafter. Not more than a 10% rate of cure was obtained in patients with Pseudomonas infections. There was a low rate of cure in patients with infections caused by Proteus mirabilis, which has been found [2] to be the commonest species of Proteus. Less than 20% of infections due to these three pathogens were eradicated. The best results were obtained in patients with infections caused by Escherichia coli, Aerobacter aerogenes, Paracolobactrum, intermediate coliform bacteria, Klebsiella, and staphylococci, although this last organism is usually found mixed with one of the gram-negative bacilli.

The original organism was eradicated in about 60% of these patients but there was emergence of another genus in about one-third, either during or a short time after completion of therapy. After trying various dosage schedules we established as a routine 0.5 Gm. of kanamycin every 12 hours for six days, although 1 Gm. every 12 hours is indicated in a patient with suspected or proved bacteremia. The spectrum of kanamycin is identical with that of neomycin but with less nephrotoxicity and ototoxicity, although the incidence of the latter is high when the drug is used for a long period of time, such as for tuberculosis, and there is an increased danger when 2 to 3 Gm. is given daily in short-term courses.

Resistance is said to develop more slowly to kanamycin than to other broad-spectrum antibiotics, but undoubtedly it will be a factor in the future. It has already been demonstrated that resistance develops quite readily in tubercle bacilli in patients who are subjected to treatment with the drug for long periods. We have noted frequently, in patients with infections caused by gram-negative bacteria which were not cleared up by kanamycin, that there has been an increased resistance in vitro even though the period of administration was relatively short.

Factors Influencing Therapy

The clinical types of patients selected for long-term therapy were chiefly those with chronic recurrent urinary tract infections without associated uropathy and some patients with neurogenic bladders. Our results chiefly concerned observations on 34 adults and 4 children to whom cycloserine (Seromycin) [3] was administered for from six months to three years and in whom it has proved to be quite satisfactory. There were comparatively few side-reactions with the amount of drug needed to control these infections. In some instances cultures remained positive during the administration of cycloserine but the patients usually remained asymptomatic and without pyuria. The most common organisms to persist were enterococci and Proteus mirabilis, but these bacteria were in small numbers and did not cause significant pyuria. The original inoculum frequently showed no growth on solid medium but was obtained only after the urine was incubated overnight.

Many of these patients undoubtedly had chronic pyelonephritis, diagnosis of which is frequently difficult to make.

Martin and co-workers,[4] in a recent excellent review of infections in the urinary tract, stated that renal biopsy revealed that the proportion of normal biopsy specimens decreased with the duration of infection; in only 10% of patients with chronic infection did biopsy reveal normal tissue. Yet those patients who are not treated may be subjected to progressive damage of the kidneys. It would be logical to assume that antibacterial therapy may offset this damage in many instances.

Another medicament, nitrofurantoin (Furadantin), has given encouraging results in a few adult patients to whom it was given in a total dosage of 3 mg. per kilogram of body weight per 24 hours in divided doses three or four times daily. Marshall and Johnson [5] reported successful results with prolonged administration of nitrofurantoin in chronic infections in children, as have Lippman and his co-workers [6] and Norfleet [7] in adults.

Intermittent therapy is indicated chiefly in those patients with chronic urinary infections associated with demonstrable uropathy and chronic pyuria, especially if there are frequent episodes of clinical exacerbation. A simple and often reliable method of evaluating therapy is the gross appearance of the urine supplemented by microscopic examination. Failure of the urine to clear within two or three days of therapy is an indication either of wrong choice of drug or of some underlying pathological factor. The sulfonamides are quite satisfactory for this purpose if there is favorable and tolerable response to their administration. Some urologists have advocated treatment one week of each month and others administration every other week. Usually this type of therapy requires full dosage during the period of treatment. Recently we have had some encouraging results in patients to whom sulfonamides were given every other day or every third day, depending on the duration of the favorable response after discontinuance of therapy with the drug. Methenamine mandelate is another drug of value for interrupted administration to a patient in whom the response is favorable.

There are certain types of infections in which therapy is indicated only during clinical exacerbation. Patients with such infections have chronic pyuria with little or no response during treatment. Common examples of these infections are nonremediable calculous disease of the urinary tract, infections after transureteral resection for carcinoma of the prostate, noncorrectible anomalies, and some small-caliber strictures.

Antimicrobial therapy appears to be of value in patients with chronic uncomplicated nonspecific prostatitis when the infecting organism is a known pathogen, such as Staphylococcus aureus or any of the gram-negative bacilli. Here it is of value to do sensitivity tests for selection of the best drug to be used. Acute uncomplicated prostatitis is comparatively rare, with Esch. coli the most common infecting organism, and it generally responds to sulfonamide therapy in adequate dosage. If the chronic prostatitis is secondary to associated disease, corrective surgery should be done, if possible. Otherwise, treatment should be limited to control of infection during clinical exacerbation.

Drugs in Combination

The best documented reason for the use of two agents is an infection caused by both bacillary and "coccic" organisms; what may be the best drug for one may not be the best for the other. These infections often have proved resistant to cure and, if they are chronic, there is ample time for sensitivity tests to aid in the selection of two or more medicaments.

There is apparent reduction of side-reactions to either of two drugs when they are given in smaller dosage. For instance, when novobiocin is administered in a dose of 1 Gm. per day for longer than six days there is a high incidence of dermatological manifestations, but when 0.5 Gm. is given in combination with another anti-infective drug there is a decreased incidence of side-reactions. Also, when oleandomycin is combined with a sulfonamide, each in one-half of the maximum dosage, there appears to be better tolerance to both drugs in most patients.

Synergism or potentiation has been proved in connection with the administration of penicillin and streptomycin for streptococci, notably enterococci. Also, there seems to be increased efficacy when streptomycin and chloramphenicol are administered in combination for Proteus infections. Streptomycin given in combination with tetracycline or terramycin often produces successful results in Pseudomonas infections when either one alone fails to cure. Any of these combinations presupposes that the infecting organism is sensitive or at least partially sensitive to both medicaments. We have noted frequently that when Pseudomonas has been resistant to tetracycline in vitro, it will be sensitive or partially so to terramycin.

A common example of a means of delaying or preventing the emergence of resistant organisms is the use of PAS (para-aminosalicylic acid) in combination with streptomycin and isoniazid; generally such a combination is more effective than either drug alone. We have had encouraging results in a few patients with tuberculosis of the urinary tract to whom cycloserine, 250 mg. twice daily, was given in combination with isoniazid, 150 mg. twice daily. One patient with unilateral renal tuberculosis of long duration has had negative cultures, which produced no infection in guinea pigs for nearly two years after the discontinuance of the combined therapy. Cultures from a few others have produced a negative reaction in guinea pigs but either these patients are still on combined therapy or medication has been discontinued too recently to be certain that there might not be a reversion to positive reaction later. The combination of cycloserine and biomycin has recently been reported by Ståhle[8] to be of great value in the treatment of pulmonary tuberculosis. Epstein and co-workers[9] reported that the neurotoxicity of cycloserine was reduced markedly when pyridoxine (300 mg. per day) was given in connection with cycloserine, even though 2 Gm. daily of the latter drug was given for periods of one year or more. Lattimer[10] stated that pyridoxine, 50 mg. twice daily, must be given to patients receiving isoniazid.

25 E. Washington St. (2) (Dr. Herrold).

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OXALATE URINARY TRACT STONES

Jack Hughes, M.D., William M. Coppridge, M.D.,† Louis C. Roberts, M.D.
and
Virgil I. Mann, Ph.D., Durham, N. C.

Urinary calculi were found in 4,500 hospital patients during a period of thirty-five years. Studies were made on 2,693 such stones either recovered clinically or removed at autopsy. The stones were found oftener in men than in women and oftener in the ureter than in the kidney. They were analyzed by petrographic crystallography. Calcium oxalate was the major mineral component of most of the stones encountered. Oxalate stones occurred more frequently in men and phosphate stones more frequently in women. About 20% of the oxalate stones were readily identifiable as primary, in the sense of having formed on a renal papilla, for they bore a definite indentation as if molded over a papilla and had a rough depression marking the point of attachment. The rate of 25 urinary stones per 1,000 patients discharged from this hospital was more than three times the estimated national average but is believed to be representative of the southeastern part of the country, which includes North Carolina.

The southeastern United States is one of the principal "urinary stone areas" of the world,[1] and during the period 1922-1957 we encountered approximately 5,400 urinary tract stones in 4,500 native-born patients. The current rate in Watts Hospital of 25 urinary stones per 1,000 discharges is more than three times the estimated national average.[1] A group of the stones recovered clinically and the primary oxalate stones found in a series of autopsies on adults were studied by some of the techniques currently available. Observations based on the results of these studies and a discussion of some of the current views on oxalate stone formation are presented.

The distribution of 2,693 stones on the basis of sex and anatomic locations is as follows: in the ureters, 1,400 in male and 643 in female patients, for a total of 2,043; in the kidneys, 321 in male and 329 in female patients, for a total of 650. A preponderance of ureteral stones with greater incidence in the male is evident.

The distribution of 287 unselected stones on the basis of sex of patient and major mineral content is shown in table 1. The factor of anatomic location is not considered, since deletion does not alter the results significantly. All stones were analyzed by petrographic crystallography and a quantitative estimate was made of mineral content. The monohydrate and dihydrate calcium oxalate stones are listed under oxalate; the apatites and magnesium ammonium phosphate are grouped under phosphates. Most of the oxalate stones contained more than 90% of one or both oxalates and all so classified contained more than 75%. Eight mixed oxalate-phosphate stones containing less than 75% oxalates were included in the phosphates group.

It is evident from the results in table 1 that calcium oxalate is the major mineral component of most of the stones encountered and that oxalate stones occur more frequently in male and phosphate in female patients.

The trademark of the stone belt is the primary oxalate stone (fig. 1 and 2). This term is used to describe those stones composed almost entirely of oxalate (usually monohydrate) which form on a renal papilla, usually in acid urine, in the absence of infection. When such a stone becomes detached there is a definite indentation where the stone has grown, as if it were molded over the papilla. A small, shallow, rough depression near the center of the indentation is often seen and represents the point of attachment (origin). About 20% of the oxalate stones were readily identifiable as being primary. However, this percentage does not represent the true incidence, since a primary stone often serves as a nidus for the formation of larger oxalate, phosphate, and even uric acid stones.

At least one primary oxalate stone was found in 13 of 126 autopsies done on native-born adults (table 2). The ages of the 13 ranged from 33 to 84 years.

The higher incidence of oxalate stones in men is again demonstrated in this small series. Further studies are being carried out on this type of primary stone in an effort to learn more about the mechanism of formation.

The phosphate content of "pure" primary oxalate stones was investigated. Ten primary stones measuring up to about 0.5 cm. in the largest diameter were analyzed by petrographic crystallography and x-ray diffraction; no phosphate was found. However, quantitative chemical analysis done on five of the same stones revealed a phosphate content of from 0.74 to 5.0% of dry weight. Whether this small amount represents phosphate "absorbed" from the urine in which the stone has been bathed or is a necessary part of oxalate crystallization has not been determined.

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†Dr. Coppridge died Aug. 28, 1959.

From the Department of Urology, Watts Hospital, and the Department of Geology, University of North Carolina.

Read before the Section on Urology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 12, 1959.

TABLE 1.—*Mineral Content of 287 Stones Found in Unselected Patients*

	Oxalate	Phosphate	Uric Acid	Total
Male	169	20	3	192
Female	52	41	2	95
Total	221	61	5	287
%	77	21.2	1.8	100

The incidence of hyperparathyroidism in our patients with stones was less than 0.5% and therefore should not alter significantly any of the statistics presented.

Comment

The mechanism of the formation of oxalate as well as other primary and secondary urinary stones has been studied extensively. Randall[2] found that primary stones form on a renal papilla on a small subepithelial calcium plaque which has lost its thin epithelial covering or on a nidus of inspissated calcium salts in a papillary tubule. Vermooten[3] presented evidence to show that calcium salt deposition takes place in any of the collagen fibers in the renal papilla—interstitial connective tissue, basement membrane of the collecting tubules, and the circular fibers surrounding the small blood vessels. Any of these deposits may ulcerate through and lead to stone formation.

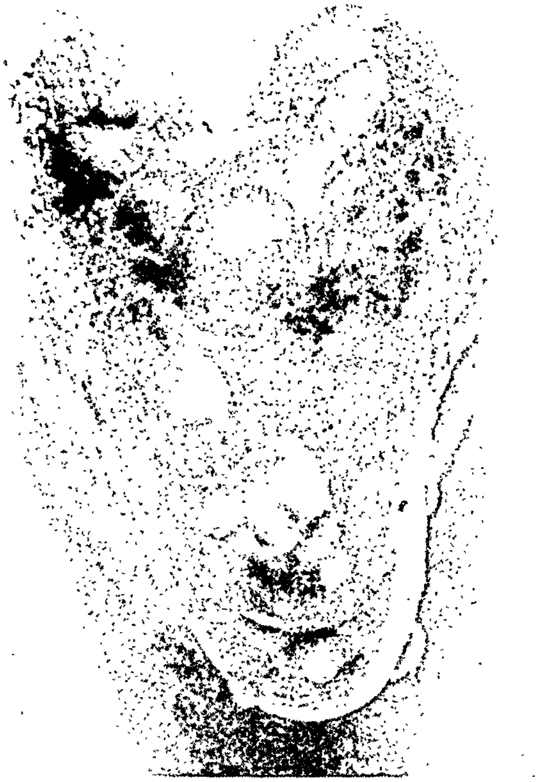

Fig. 1.—Primary oxalate stone, 1.0 cm. in largest diameter, showing typical indentation (×3).

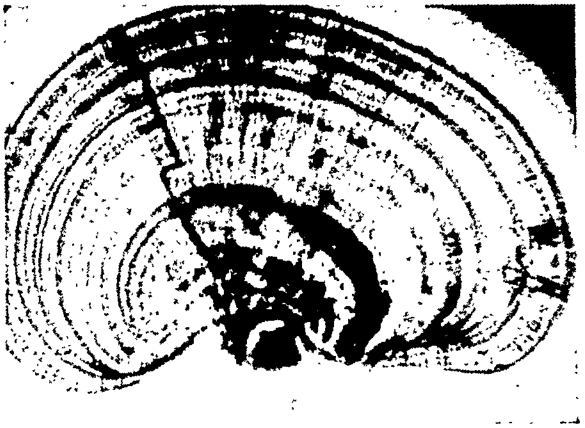

Fig. 2.—Primary oxalate stone, 3 mm. in diameter, embedded in plastic and ground to thickness of about 100 μ (×48).

In 1954 Howard[4] pointed out that a "ground substance" with staining properties similar to bone matrix had been found in some urinary stones. He suggested that since the properties of matrix apparently govern the initiation and orientation of the crystal structure of bone perhaps the matrix of at least some of the urinary stones might serve the same purpose. After extensive studies of stone matrix Boyce and King[5] concluded that the "presence of a crystallizable matrix is thus the essential phase in concrement formation." They consider matrix to be the determinant of crystal position, crystal composition, and gross stone structure and possibly a factor in the recrystallization of some stones.

It has been well established that hyperoxaluria is not a factor in the formation of most oxalate stones; the exceptions are in those patients with primary oxalosis and possibly in certain patients with sarcoidosis.[6]

TABLE 2.—*Oxalate Stones Found in Adults at Autopsy*

	No.	Primary Stones	%
Men	68	11	16.3
Women	58	2	3.5
Total	126	13	10.3

It has been proposed by many investigators[7] that all oxalate in urinary stones is first deposited as the more soluble dihydrate; when a molecule of water is lost the mineral becomes monohydrate. We have found nothing clinically to support such a thesis. Crystals of the two types are seen frequently in close approximation during the course of petrographic analysis, and the margins are always distinct. There are instances of geological formation in which a crystal structure is changed by a loss or gain of one or more molecules of water, but in such instances definite stages of transition can be demonstrated. We believe that the two types of oxalate encountered in urinary stones develop independently under different physiochemical conditions.

The greater incidence of oxalate stones in male and phosphate stones in female patients encountered in the study needs to be explained. Possibly the reason is related to hormonal activity or a sex-linked genetic factor. However, two simple explanations are worthy of consideration. (1) Male and female subjects probably have the same defect causing oxalate stone formation; the activities of the male subject at both work and play make him more readily affected by such environmental factors as heat, humidity, and stress. (2) The higher incidence of phosphate stones may be related to the higher incidence of urinary infections in female subjects.

Certain factors such as diet, infection, urinary pH, hydration, and levels of urinary calcium are known to exert some influence on stone formation, but the basic abnormality causing matrix to be formed and the particular physiochemical environment determining which mineral is to be deposited in or on the matrix remains unknown.

Summary

The southeastern United States is one of the principal "urinary stone areas" of the world, and the major mineral component of most of the stones is calcium oxalate. Oxalate stones occur more frequently in male than in female subjects. Certain factors are known to exert some influence on stone formation, but the basic cause (or causes) remains unknown.

1200 Broad St. (Dr. Hughes).

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PERIODONTAL DISEASE AND DIABETES IN YOUNG ADULTS

Capt. Ralph C. Williams Jr. (MC)
and
Major Charles J. Mahan (DC), U. S. A. F.

The observation that chronic infection predisposes to difficulty in regulation of diabetes is a concept which has been stressed by numerous authors.[1] Infection and inflammatory reactions may increase insulin requirements in a previously stable diabetic patient.[2] Much attention has been devoted in the past toward control of indolent urinary tract infections [1c] or skin infections [3] among patients with diabetes; however, relatively scanty regard has been directed at systematic eradication of chronic periodontal disease among diabetics.

Purpose of Study

Recently we have been impressed by the striking frequency with which the relatively young diabetic patients seen in a military practice manifest extensive periodontal disease which heretofore had been undiagnosed and untreated. This is, in fact, an observation to which numerous references have been made since 1899, when Grunert [4] stressed the association of far-advanced pyorrhea with diabetes mellitus. In 1928, Williams [2b] described a group of oral conditions which he termed diabetic periodontoclasia. His observations among 58 diabetic pa-

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From the departments of internal medicine and periodontology, U. S. A. F. Hospital, Maxwell Air Force Base, Air University, Montgomery, Ala. Dr. Williams is now on the staff of the Medical Service, Massachusetts General Hospital, Boston.

tients suggested that gingival and periodontal disease among this group constituted a distinct clinical entity. Later, Hirschfeld[5] described acute gingival abscesses and pedunculated marginal gingiva as being conditions intimately associated with diabetes mellitus. In 1938, Rudy and Cohen[6] described oral pathology among a group of 403 patients with diabetes. These authors noted a high incidence of diffuse alveolar atrophy among the younger patients and considered the periodontal symptoms as one of the manifestations of diabetes—in the same category as pruritis vulvae or transient visual disturbances. However, Glickman[7] in 1946 noted no changes in the gingival tissue or the periodontal membrane of experimental animals with alloxan-induced diabetes, although demineralization of the alveolar process was evident. Other authors[8] support the view that manifestations of periodontal disease seen in diabetics are not specific disease entities but are the results of local irritation in the presence of decreased systemic resistance.

Methods and Results of Periodontal Treatment in Nine Young Adult Diabetics

Patient		Duration of Diabetes, Mo.	Insulin Requirement Before Treatment	Range of Blood Sugar Levels Before Treatment, Mg. %	Periodontal Treatment*	Oral Pathology	Length of Observation Postoperatively, Mo.	Insulin Requirement After Treatment	Range of Blood Sugar Levels After Treatment, Mg. %
Age, Yr.	Sex								
20	M	6	75 units U-80 NPH 10 units regular	280-430	Extraction: 1, 2, 16, 17, 32. Scaling and curettage: 3-15, 18-30.	Chronic marginal gingivitis	3	60 units U-80 NPH 10 units regular	110-120
32	M	5	55 units U-40 NPH 15 units regular	200-230	Extraction: 2-12, 16, 30-31. Gingivectomy remaining mandibular teeth.	Chronic gingivitis and periodontitis	3	20 units U-40-NPH 10 units regular	70-120
32	M	96	90 units U-80 NPH 15 units regular	200-350	Extraction: 1, 3, 28-29, 16. Scaling and curettage remaining teeth.	Chronic marginal gingivitis; pulpitis 28-29.	3½	55 units U-80 NPH 10 units regular	135-190
25	F	36	50 units U-40 NPH	210-315	Extraction: 11, 13, 16, 32. Gingivectomy: 14-15, 19-21, 28-31.	Chronic marginal gingivitis; periapical abscess 13	7	45 units U-80 NPH	200-246
20	M	4	85 units U-80 NPH	200-250	Extraction: 1, 16. Gingivectomy: 1-4, 13-17. Scaling and curettage: 5-12, 17-32.	Chronic marginal periodontitis	3	32 units U-80 NPH	120-140
30	M	36	50 units U-80 NPH	125-160	Extraction: 1, 5-17, 32. Gingivectomy all remaining teeth.	Chronic marginal periodontitis	3	38 units U-80 NPH	125-140
26	M	7	None—diet alone	130-150	Gingivectomy: 2-3, 10-15, 20-23, 27-29. Scaling and curettage all remaining teeth.	Chronic marginal periodontitis	3	No insulin, but 1 Gm. of tolbutamide (Orinase) per day	150-175
23	M	2	75 units U-80 NPH	150-165	Gingivectomy: 1-3, 11, 22-32. Scaling and curettage: 5-7, 10-16, 17-21.	Chronic marginal periodontitis	3	25 units U-80-NPH	105-140
30	M	2	35 units U-40 NPH	150-180	Gingivectomy: 1-6, 15, 23-26. Scaling and curettage: 8-16, 20-28	Chronic marginal periodontitis	3	15-25 units U-40 NPH	120-150

* Teeth are numbered consecutively, beginning with maxillary right third molar through maxillary left third molar as 1 through 16, and beginning with mandibular left third molar through mandibular right third molar as 17 through 32.

With the present multipurpose insulins and antibiotic support, it has become possible to treat periodontal pathology on an inpatient status, with use of surgical procedures where indicated.[9] It is the purpose of this study to describe systematic therapy of periodontal disease among a group of diabetic patients and to study the effects of these procedures on the patient's insulin requirements, diabetic control, and periodontal health.

Materials and Methods

A group of nine patients was selected from the diabetics routinely admitted or referred to the U. S. A. F. Hospital. Patients were chosen for study after control of diabetes had been accomplished by standard methods of diet and administration of insulin or orally given hypoglycemic agents. All patients manifested gross evidence of periodontal disease on initial physical examination and were referred to the periodontist for examination, diagnosis, and planning of their treatment. After stabilization of insulin requirement and diabetic program, appropriate periodontal treatment and oral surgical procedures were carried out under local anesthesia as one procedure. Exposed gingival margins subsequently were protected by periodontal surgical dressings, until healing had progressed. When gingival surgery was indicated, no limitation was placed on the amount of tissue treated at one operation. If indicated, total gingivectomy was performed in addition to necessary extractions. In fact, experience indicated that treatment of dental pathology at one fell stroke proved advantageous in selected cases. Antibiotic therapy, with use of 300,000 units of procaine penicillin G and 0.5 Gm. of streptomycin given intramuscularly twice a day was maintained for an average of 10 days in each patient subjected to treatment. Diabetic diets were continued during convalescent periods, with appropriate use of liquid and semisolid foods until gingival healing allowed return to normal foods, usually after 10 days. Each patient was followed up closely both preoperatively and postoperatively by the internist. Preoperative and postoperative therapy was coordinated between the periodontist and the internist, and close interdepartmental liaison was maintained for all patients treated. Insulin requirements and the state of diabetes were studied for a minimum of three months in each patient subjected to treatment.

Results

Seven of the nine patients with diabetes and periodontal disease who underwent elective periodontal therapy showed significant subsequent reduction in insulin requirement. The average reduction in insulin dosage was 30 units of isophane (U-40, NPH) insulin, with a range of 10 to 55 units. One patient showed no change in her insulin requirement, despite extraction of four nonvital teeth and extensive periodontal therapy. One patient with mild diabetes which originally had been controlled by diet alone later required oral administration of hypoglycemic agents for diabetic regulation. This was attributed to improvement in his eating habits after alleviation of pain in his gums. Diets and caloric intakes in all other patients were not changed significantly during the course of the study. The results are summarized in the table.

Comment

An old concept has been reused to advantage, as oral inflammation and infection were surgically and medically attacked among this small group of diabetic subjects. There is considerable theoretical conflict concerning the etiology of periodontal disease and gingivitis in all patients with or without diabetes mellitus. No characteristic organism or bacterial flora ever has been consistently implicated as causing periodontal inflammation. In the diabetic patient nutritional factors, such as subclinical vitamin deficiencies or previous periods of acidosis, may have featured as initial factors impairing local gingival metabolism. Resorption of alveolar bone and local abscess formation among the diabetics studied may have been on a neurogenic basis; however, there was no correlation between dental pathology and diabetic neuropathy. It is our clinical impression that diabetes mellitus and chronic, destructive periodontal disease are separate entities. Diabetes may be adversely influenced by the presence of periodontal disease, and conversely periodontal disease may be more severe in the diabetic state.

Trials of preoperative antibiotics for periods of 3 to 10 days in patients subjected to surgical treatment of periodontal disease produced no change in insulin requirements or in the state of diabetes. It was only after elective surgery had been accomplished that significant improvement in diabetic control was notable. It is therefore suggested that careful oral evaluation and periodontal survey be conducted in every diabetic patient.

Summary

Gingival and periodontal disease are common in young diabetic patients. Treatment of oral pathology by elective periodontal surgery and extractions where indicated may improve the practical regulation of diabetic patients. Periodontal therapy need not be confined to treatment of small areas. Treatment of the total pathology at one operation proved beneficial in selected patients.

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COMPARISON OF ACUTE HYPOGLYCEMIC POTENCIES OF TOLBUTAMIDE AND CHLORPROPAMIDE

James W. Craig, M.D., Max Miller, M.D., Frank D. Mills
and
Naomi Nickerson, B.S., Cleveland

Tolbutamide and chlorpropamide were compared as to their intrinsic hypoglycemic action by statistical analysis of data obtained from 21 diabetic patients. The hypoglycemic agents, usually taken orally, were administered intravenously to avoid their possible differences in rate or completeness of gastrointestinal absorption. The blood specimens were drawn from the patients during three hours after administration of the drugs to assure comparison of their hypoglycemic effect at a time when the plasma concentrations would be similar. The specimens were analyzed for blood glucose and plasma levels of the two drugs. Each patient was tested once with each drug. The two drugs were found not to differ in their acute hypoglycemic potencies, and the need for a greater dosage of tolbutamide in long-term therapy is most likely explained by its more rapid rate of inactivation and excretion.

At present two sulfonylurea drugs are available in the United States for clinical use as orally administered hypoglycemic agents. These compounds, tolbutamide (Orinase) and chlorpropamide (Diabinese), are similar in chemical structure, are effective in the same general types of diabetic patients, and probably have a common mechanism of action. However, the orally given dose of chlorpropamide, which is effective in the prolonged therapy of diabetes mellitus, is usually less than that of tolbutamide.[1] The smaller dose requirement of chlorpropamide than of tolbutamide might be due to differences in the gastrointestinal absorption of the two drugs, differences in their rates of inactivation or excretion, or different intrinsic hypoglycemic potencies. In the present investigation the intrinsic hypoglycemic potencies of the two drugs have been compared. The drugs were administered intravenously to avoid the effect of possible differences in the rate or completeness of their gastrointestinal absorption. The studies were limited to three hours after administration of the drugs so that their blood glucose-lowering effects might be compared at a time when plasma concentrations of the drugs were similar; the influence of different rates of inactivation and excretion of the two drugs was thus eliminated.

Methods

The subjects for these studies were 21 hospitalized patients with diabetes mellitus. The diabetes was of the stable type in all subjects, with the possible exception of the patient in case 4, who had chronic pancreatitis. Each patient was tested at least twice, once with tolbutamide and on another occasion with an equal dose of chlorpropamide; doses of 1.0, 0.5, 0.25, or 0.125 Gm. of the sodium salts of the compounds were used. Patients 11 and 12 were tested at more than one dose level of the two drugs. The tests were performed with the patients resting in bed after fasting overnight. At the beginning of the test the subjects were free of the influence of exogenous hypoglycemic agents; they had received no long-acting insulin for at least 48 hours, no regular insulin for 15 hours, no tolbutamide for 15 hours, and no chlorpropamide for at least 96 hours before any of the tests. A 5% aqueous solution of the sodium salt of the drug was injected into a peripheral vein in one minute. Blood samples were obtained through an indwelling needle in a peripheral vein before and at 30-minute intervals after drug administration for a total of three hours. Blood glucose concentrations were determined by the colorimetric method of Somogyi[2] and plasma tolbutamide and chlorpropamide levels by the method of Toolan and Wagner.[3]

Ten replicate glucose determinations performed on each of three different samples of blood yielded a mean standard deviation of ±4.1 mg. per 100 ml.; the glucose concentrations of the three samples ranged from 108 to 122 mg. per 100 ml. Replicate determinations of tolbutamide in plasma gave an average standard deviation of ±1.1 mg. per 100 ml. at plasma levels of 2 to 20 mg. per 100 ml., and the corresponding figure for chlorpropamide was ±0.6 mg. per 100 ml. at levels of 1 to 20 mg. per 100 ml. The statistical significance of differences between blood glucose responses to the two drugs and between their plasma levels was assessed by analysis of the differences of paired observations.[4]

From the Department of Medicine, the School of Medicine, Western Reserve University.

TABLE 1.—*Decreases in Blood Glucose Concentration Produced by Intravenous Administration of Equal Quantities of Sodium Tolbutamide (T) or Sodium Chlorpropamide (C) to Same Diabetic Patient.*

Subject	Drug Administered	Fasting Blood Sugar, Mg./100 Ml.	Blood Glucose Decrease, Mg./100 Ml., Minutes After Administration					
			30	60	90	120	150	180
			Dose: 1.0 Gm.					
1	T	165	..	10	..	46	..	65
	C	153	..	21	..	43	..	62
2	T	195	..	26	..	51	..	75
	C	182	..	37	..	62	..	..
3	T	184	24	34	45	62	..	75
	C	150	11	21	24	35	..	60
4	T	347	39	33	42	41	..	67
	C	337	0	12	30	18	..	46
5	T	234	— 5	13	38	50	..	56
	C	188	6	22	31	47	..	68
6	T	156	2	15	28	32	..	56
	C	155	17	33	43	53	..	53
7	T	96	13	23	29	29	..	32
	C	103	20	30	36	44	..	49
8	T	120	— 4	8	15	18	..	37
	C	119	4	10	19	28	..	52
Mean*	T	187	11.5	20.2	32.8	41.1	..	55.4
	C	173	9.7	23.2	30.5	41.3	..	55.7
	T-C†		1.8±8.4	—3.0±4.7	2.3±5.4	—0.2±6.2		—0.3±5.7
			Dose: 0.5 Gm.					
9	T	263	— 3	— 4	6	15	..	41
	C	268	20	29	36	46	..	62
10	T	171	..	19	17	33	53	45
	C	149	20	19	33	38	..	..
11	T	265	8	29	31	38	53	55
	C	264	8	17	27	32	40	57
12	T	152	2	16	17	25	26	34
	C	144	6	23	32	37	40	..
13	T	165	17	23	42	59	62	69
	C	175	12	26	30	33	50	53
14	T	136	10	15	20	28	26	29
	C	145	7	10	18	26	32	32
Mean*	T	192	6.8	16.3	22.2	33.0	41.7	48.5
	C	191	10.6	20.7	29.3	35.3	40.5	52.8
	T-C†		—3.8±5.1	—4.3±6.3	—7.2±6.4	—2.3±7.8	1.2±6.7	—4.3±7.8
			Dose: 0.25 Gm.					
15	T	114	14	20	30	34	..	33
	C	93	3	11	10	16	..	12
16	T	119	17	23	33	32	..	14
	C	125	..	23	25	27	38	27
12	T	170	3	15	26	26	32	32
	C	180	3	12	23	26	28	44
17	T	197	11	14	25	..	16	26
	C	178	11	15	21	25	32	32
18	T	175	17	21	27	34	41	51
	C	176	2	16	18	30	42	39
Mean*	T	155	11.3	18.6	28.2	31.5	29.7	31.2
	C	150	4.8	15.4	19.4	24.7	34.0	30.8
	T-C†		6.5±3.8	3.2±3.2	8.8±3.0‡	6.8±3.9	—4.3±6.0	0.4±6.8
			Dose: 0.125 Gm.					
12	T	184	7	10	28	35	36	42
	C	178	2	..	13	21	28	35
11	T	219	6	10	19	27	31	36
	C	226	10	..	17	20	26	41
19	T	130	7	11	16	16	16	14
	C	149	14	22	30	29	22	19
20	T	165	7	12	29	35	56	58
	C	178	8	20	30	42	52	59
21	T	201	— 8	5	11	16	25	36
	C	225	— 2	7	11	19	31	47
Mean*	T	180	3.8	9.3	20.6	25.8	32.8	37.2
	C	191	6.4	16.3	20.2	26.2	31.8	40.2
	T-C†		—2.6±2.5	—7.0±5.0	0.4±4.6	—0.4±4.9	1.0±3.0	—3.0±3.0

* In the calculation of the mean blood glucose decreases, a value was omitted if no corresponding value was available at the same time interval in the test with the other drug.

† Mean of individual differences (± one standard error) between blood glucose decreases after administration of tolbutamide and after that of chlorpropamide.

‡ Probability of greater than 95% that blood glucose decreases after administration of tolbutamide and chlorpropamide are different.

Results

As shown in table 1 and the figure, at all four dose levels, equal quantities of tolbutamide and chlorpropamide produced similar decreases in the blood glucose concentration during the three hours after drug administration. At no point did chlorpropamide exhibit a significantly greater hypoglycemic effect than tolbutamide. The mean plasma concentrations of the two drugs are shown in table 2. After two and three hours the average tolbutamide levels were usually slightly less than the chlorpropamide levels, but the differences were not statistically significant except at 180 minutes after administration of the 0.125 Gm. dose. At no time was the plasma concentration of tolbutamide significantly greater than that of chlorpropamide.

Table 2.—*Mean Plasma Concentrations of Tolbutamide (T) and Chlorpropamide (C) After Intravenous Administration of Equal Quantities of Sodium Salts of Drugs to Same Diabetic Patients*

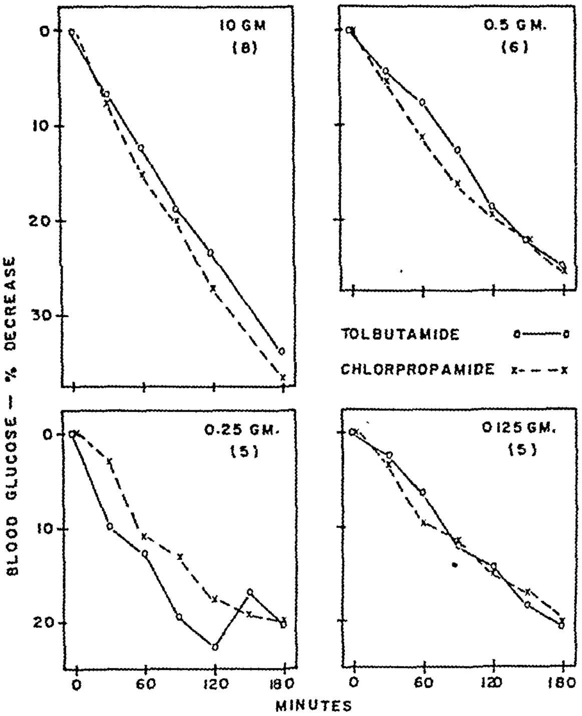
Dose of Drug, Gm.	No. of Subjects	Drug Administered	Concentration of Drug in Plasma, Mg./100 Ml., Minutes After Administration: 60	120	180
1.0	8	T	9.9	7.7	6.8
		C	8.8	8.5	8.1
		T-C*	1.1±1.2	−0.8±1.8	−1.3±1.0
0.5	6	T	6.3	3.7	2.7
		C	6.8	4.6	3.5
		T-C*	−0.5±1.0	−0.9±0.9	−0.8±0.8
0.25	5	T	4.2	2.8	1.6
		C	2.6	2.1	1.8
		T-C*	1.6±0.5	0.7±1.6	−0.2±0.9
0.125	5	T	2.1	1.1	0.6
		C	3.4	1.7	2.4
		T-C*	−1.3±0.7	−0.6±0.6	−1.8±0.5†

* Mean of individual differences (± one standard error) between [illegible]amide and chlorpropamide.

[illegible] 95% that plasma concentrations of [illegible] are different.

Comment

Observations by ot[illegible]orpropamide was more [illegible] in lowering the blood glucose concentration of normal or diabetic subjects within one to five hours after oral administration [5] are probably explained by the slower gastrointestinal absorption of the latter drug [6] rather than by a difference in the intrinsic hypoglycemic potencies of the two compounds. Tornow and co-workers [7] also compared the hypoglycemic effects of 1 Gm. of tolbutamide and an equal dose of chlorpropamide by giving the drugs orally to diabetic patients; during the four hours after administration, chlorpropamide therapy produced a slightly greater decrease in the blood glucose concentration than did tolbutamide, but the difference was not considered clinically significant. The results of subsequent studies by West,[8] in which the compounds were administered intravenously to normal subjects, confirm the finding of the present study that at equal plasma levels of the two drugs their acute blood glucose-lowering effects are of similar magnitude. Knauff and colleagues [1a] also found similar degrees of hypoglycemia during six hours after the intravenous administration of 30 mg. per kilogram of body weight of chlorpropamide or tolbutamide to normal or diabetic subjects. The same investigators [1a] reported that during long-term administration of tolbutamide or chlorpropamide to nondiabetic subjects the degree of fasting hypoglycemia was a function of the fasting serum sulfonylurea level and that on the basis of serum concentrations the two drugs were equally active as hypoglycemic agents. The findings of Forsham and co-workers,[1b] that lower serum levels of chlorpropamide are required for significant hypoglycemic effects as compared to tolbutamide, and the report of Stowers and colleagues,[8] that at the same blood level chlorpropamide produces a greater fall in the blood sugar level than tolbutamide, are difficult to reconcile with the results just described; neither of the reports states clearly whether these conclusions are drawn on the basis of comparisons of the two drugs in the same or in different subjects. However, most available evidence indicates that in the long-term therapy of diabetes mellitus the lower dosage requirement for chlorpropamide as compared to tol-



Comparison of acute hypoglycemic potencies of tolbutamide and chlorpropamide; mean decreases in blood glucose concentration produced by intravenous administration of equal doses of sodium salts of tolbutamide and chlorpropamide to same diabetic patients. Decreases are expressed in terms of percentage of fasting blood glucose concentrations. Number of patients tested with each dose of drugs is indicated in parentheses.

butamide is not explained by a difference in the intrinsic hypoglycemic potencies of the two compounds but by a slower rate of inactivation and excretion of the former drug[9]; as a result, higher serum drug levels are produced and maintained by a given dosage schedule of chlorpropamide.

Summary

Blood glucose concentrations and plasma drug levels were measured for three hours after the intravenous administration of tolbutamide (Orinase) or chlorpropamide (Diabinese) to diabetic patients. Each subject was tested twice, once with tolbutamide and on another occasion with an equal dose of chlorpropamide. At all four dose levels (1.0, 0.5, 0.25, and 0.125 Gm. of the sodium salts of the drugs) similar plasma drug levels and a similar lowering of the blood glucose concentration were produced by the two drugs. It is concluded from these results, and from the longer term studies of other investigators, that the two compounds probably do not differ in their intrinsic hypoglycemic potencies. The lower dosage requirement of chlorpropamide as compared to tolbutamide therapy is due to the higher blood drug levels maintained by a given dosage schedule of chlorpropamide.

2065 Adelbert Rd. (6) (Dr. Miller).

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The tolbutamide used in this study was supplied as Orinase by The Upjohn Company, Kalamazoo, Mich., and the chlorpropamide was supplied as Diabinese by Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

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NEED OF PSYCHOTHERAPY IN DIABETES.—Many young diabetic patients exhibit a gamut of unreasonable behavior which can be interpreted as essentially self-destructive. While similar behavior may occur in adult diabetics and in other chronic illness, it is in the young patient with diabetes in whom a conscious or unconscious self-destructive reaction to life problems is most prominent. Various aspects of the treatment of diabetes and the possible complications of the disease afford such patients ready means for self-destructive acting out. Such behavior is most frequently exhibited when major life adjustments must be made, and are more likely to occur when the emotional and socioeconomic environment is suboptimal. It is therefore essential in the treatment of juvenile diabetic patients to investigate the early manifestations of such behavior and to attempt to avoid more serious difficulties by manipulation of the environment and by a gentle, gradual adjustment of the young diabetic to a more realistic view of his illness and his problems. Since the situation is usually irretrievable when self-destructive ways of handling diabetes have become an accustomed behavior pattern, it would be desirable to interview young diabetics psychiatrically at the onset of the disease and periodically thereafter.—S. Stearns, M.D., Self-destructive Behavior in Young Patients with Diabetes Mellitus, *Diabetes*, Sept.-Oct. 1959.

RETURN TO WORK OF PATIENTS WITH ANGINA PECTORIS AND/OR MYOCARDIAL INFARCTION

Robert S. Green, M.D.
and
Erna L. Borousch, M.D., Cincinnati

In the experience of the authors it has never been necessary to resort to surgical procedures to relieve a patient of anginal attacks. Considerations here outlined have led to a program for building up collateral circulation in the coronary vessels in anticipation of eventual coronary occlusions or excessive demands on the myocardium. It is insisted that the patient be underweight. Factors inducing anginal attacks must be eliminated, and nitroglycerine must not be misused simply to escape the penalties of overburdening the heart. During subsequent rehabilitation the patient should be concerned more about returning to his job than to his advocations. In 13 years of experience with the type of patients here specified, relief from the symptoms of angina, even of the so-called intractable type, has been achieved in all patients who adhered to the plan, and most of them have returned to their former occupation.

The problem of return to work of patients with angina pectoris, myocardial infarction, or both, has been of particular interest to us in the Memorial Heart Laboratory of St. Mary's Hospital, which has every facility for advanced cardiovascular study, including surgery. The reason for our interest lies in the fact that medicine is passing through a period when heart surgeons try practically any procedure to get into this field, e. g., sprinkling of talcum powder, superimposition of omentum, anastomosis of vessels, ligation of vessels, replacement of vessels, and others. One of us (R. S. G.) has been involved in this problem since 1946, when, as a fellow, he was asked by Drs. Nicholas Carter and Johnson McGuire to obtain patients with severe angina who would be suitable candidates for a new technique of grafting lung tissue on the heart to improve collateral circulation.

The answer given in 1946 has not changed some 13 years later. We have never seen a patient with arteriosclerotic disease of the coronary arteries in whom surgery was necessary to control angina. By adhering to simple rules of living and treatment we believe these patients do a better job of growing their own collateral blood circulation than surgeons can ever hope to stimulate or implant in them. The basic considerations that led to this conclusion are as follows: 1. 77.3% of young soldiers (average age 22.1 years) on whom autopsy had been performed in Korea had gross evidence of coronary artery disease.[1] 2. If a grade 1 change is considered as minimal arteriosclerosis of the coronary arteries and a grade 4 change one where a major vessel is completely occluded, then a grade 3 change is severe. In one autopsy series of 600 cases,[2] 18% of men between 30 and 40, 40% between 40 and 50, and 75% between 50 and 70 years of age had grade 3 arteriosclerosis of their coronary arteries. In another autopsy series of 950 cases,[3] 40% of the subjects between 18 and 39, 75% between 40 and 49, and 82% of over 50 years of age had severe advanced coronary arteriosclerosis.

The conclusion to be drawn is obvious. The majority of men past the age of 20 years have arteriosclerosis of their coronary arteries, and these changes are advanced by the time these persons are 50 years of age. The answer to this problem, in the child as yet unborn, may lie in preventing such changes through diet and advanced knowledge of stress reaction, but this answer is not good enough for us or for our patients. Let us not fool ourselves—we must contend with coronary arteriosclerosis now.

The crucial and consoling fact is that practically everyone who dies at the age of 90 years has severe, advanced disease of the coronary arteries, often with occlusion of as many as five or six major vessels. Frequently such a person has never had a symptom and died from pneumonia rather than heart disease. Our hope must lie in what caused these persons to reach the age of 90 years, despite advanced disease; our concern must be why others die young, despite relatively minor changes in the coronary arteries.

A clue to the solution is found in the animal experiments of Blumgart and co-workers[4] who used a modification of the coronary artery injection technique of Schlesinger.[5] Young pigs were selected for the study because their heart circulation is com-

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From the Memorial Heart Laboratory, St. Mary's Hospital.

Read in the Symposium on Current Concepts of Heart Disease and Employment before the Joint Meeting of the Section on Diseases of the Chest and the Section on Preventive Medicine at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

parable to that of human beings. In general, when a major coronary vessel was suddenly occluded to less than 13% of the original cross-sectional area, the pigs died within 20 minutes. However, when the vessel was partially occluded at a first operation and then totally occluded some two weeks later, a significant percentage survived due to development of collateral blood vessels. In several animals the collaterals were functionally adequate and there was no gross evidence of myocardial infarction.

This is the key to the problem. It is not the occlusion of a blood vessel as such that concerns us but the extent of the collateral circulation at the time of closure. More important, an adequate collateral circulation may develop with time so that an infarction will not occur when the artery is occluded. Time, therefore, is the key to the solution. Treatment consists of reducing the work demands of the heart as much and as long as necessary to prevent any myocardial oxygen deficiency. As collateral vessels develop and the potential oxygen supply to the myocardium increases, the patients are permitted to return gradually toward a normal existence. It is important to remember that a coronary circulation that is adequate for myocardial needs at rest may be inadequate for an increased work load of the heart. This resultant unanswered oxygen deficit is considered to be the cause of angina pectoris and probably accounts for the cases of acute myocardial infarction that have been reported in the absence of fresh narrowing or occlusion.[6] A final important consideration is that the growth of collateral blood vessels is a relatively slow process.[7] Success in treatment will be in direct relation to the ability of the physician to restrict any increase of the work of the heart within the capacity of this gradually increasing circulation to deliver an adequate supply of oxygen to the potentially deficient myocardium.

Subjects and Procedures

In the clinical approach to this problem, we regard all men and those women with hypertension or diabetes as having disease of the coronary arteries. The only question we ask ourselves is whether the coronary arteries and collateral circulation are adequate to supply the oxygen necessary for the work demands placed on such a person's heart. The work load of the heart is determined by intrinsic or extrinsic factors. The intrinsic factors are too often forgotten. We can reduce the work of the heart by weight loss, lowering of high blood pressure, correction of anemia, proper control of thyroid function, supply of needed vitamins, and recognition and compensation of heart failure, particularly in the early stages when it is usually overlooked. Unusual fatigue, insomnia, or a change in the shortness-of-breath pattern may be the first evidence of cardiac failure, and digitalization often alleviates these symptoms and reduces the incidence of angina pectoris. These intrinsic factors must be considered because they are important. However, for purposes of this presentation we will consider them not present or treated.

The extrinsic factors affecting the work load of the heart stem from a world where one has to run to stand still. It is of interest that the list of factors that raise blood pressure in a normal person is comparable to the list of factors that precipitate angina, i. e., fatigue, emotion, walking, strenuous activity, meals, and cold. There is evidence that an elevation of blood pressure increases the work of the heart and results in reflex constriction of the coronary arteries. It is our concept that the transient elevations of blood pressure produced by these factors result in an oxygen deficit of the myocardium in patients with an inadequate collateral blood circulation. This deficit is usually accompanied by angina, a change in the electrocardiographic pattern, or both. This concept explains, to us at least, why angina is usually associated with a rise of blood pressure and relieved as the blood pressure falls. The easy way to facilitate a fall of blood pressure is, of course, the absorption of 1/200 grain (0.30 mg.) of nitroglycerine under the tongue.

The main approaches to the evaluation of a patient's myocardial circulation versus his cardiac work load are (1) taking a painstaking medical history, since the principal evidence of the disease is a symptom; (2) a careful physical examination; (3) laboratory studies, including an electrocardiogram and radiologic evaluation; and (4) the physiological response of the myocardium to induced strain. The importance of careful study is twofold: 1. The majority of persons are heart-conscious and have pains of one sort or another in their chest, arms, neck, and abdomen. 2. It is as serious a mistake to incorrectly diagnose angina pectoris as it is to overlook a case of angina masquerading as indigestion.

What is angina? Angina is always definite, never vague. It is usually substernal but may be manifest only by a pain in the wrist or in the region of the jaw. The patient knows when the sensation is there. He knows when it is gone. It recurs in a set pattern for any given area of oxygen deficiency in the heart. It starts in the same place, in the same way, and proceeds in the same manner. It is brought on by a definite set of factors that increase the heart's work and are learned quickly by the patient. It is relieved by eliminating these factors: if brought on by walking, it is relieved by standing still; if brought on by excitement, it is relieved by calming down. The patient learns that he can walk slowly on level ground and avoid an attack of angina. He knows that if he walks fast, uphill, or into a cold wind an attack may be provoked.

It is of interest that sensitivity to such work factors varies in individual persons. We have had patients develop angina after walking a short distance, while others can walk long distances but have an attack of angina at the slightest exposure to cold. These factors may be parlayed: a man may mow his yard without difficulty in the morning but have angina when he mows it in the evening, after a tiring day; he may walk one block without difficulty before having a meal but have angina with the same exercise, after having had a meal.

An attack of angina always lasts longer than 30 seconds and rarely longer than 15 minutes, unless myocardial infarction has occurred. It is not affected by breathing, touch, or body motions, such as twisting or bending. It does not occur at night, unless it has occurred during the day. The only exceptions we have found to the latter statement were one patient who had severe nightmares and another who was a night watchman.

This brings us to a consideration of fatigue, the most important factor of all, particularly when we consider therapy. Angina is usually an afternoon or evening disease when a patient has relatively less heart reserve, and this fatigue factor interacts with other precipitating factors. We recently saw a patient who walked to work uphill after breakfast without trouble but had an attack of angina on the way home, walking down the same hill, and who always ate at home, even though he lived alone, because the angina was worse if he ate before he walked home.

How important is fatigue? In our experience most patients who had their initial episode of myocardial infarction were in a state of chronic mental or physical fatigue at the time of the infarction. We believe fatigue not only is the earliest symptom of impending coronary insufficiency but also is the most important extrinsic factor in aggravating this condition.

If the diagnosis is clear from the history or from other findings, we usually do not perform tests that increase the oxygen need of the heart. However, when the high incidence of severe disease of the coronary arteries in males is considered, it is obvious that most patients with this potentially vicious process are without symptoms and have normal objective heart findings on physical examination, electrocardiogram, and x-ray of the chest. It is the apparently normal patient and the one who represents a doubtful case who are subjected to graded activities, accompanied by electrocardiography—the so-called tolerance tests. A two-step exercise test is performed first. If results are normal the exercise test is repeated the next day, the patient holding ice cubes in the hand; then it is repeated with ice cubes after a tiring day, and next with ice cubes after a tiring day and a large meal, and finally after a large, black cigar has been smoked. A lively argument by the patient with his wife prior to the final test is desirable. The full gamut of these tests is not routine by any means. However, if the patient survives these experiences we believe we can pat him on the back and reassure him about his coronary and collateral circulation without too much fear that he will drop dead as he leaves the office.

As stated before, we consider all men past the age of 20 years and women with diabetes or hypertension to have coronary artery disease. On the basis of these tests, their heart circulation is classified into four categories, which are as follows: 1. Those who have an adequate heart circulation. They have no symptoms or other evidence of disease and have no change in their response to heart strain. 2. Those who have an inadequate heart circulation which is manifested only by the heart strain tests. Patients in this group have no symptoms or other evidence of disease. 3. Those who have a serious deficiency of heart circulation to such a degree that they have angina, severe changes in their electrocardiograms, or both, with minimal exercise. 4. Those who have evidence of a recent myocardial infarction and thus have moved from group 3 to 4.

Treatment

Our approach to treatment is not directed toward the prevention of further coronary arteriosclerosis. We assume that this process is present and that it will progress. Our aim is to develop an adequate collateral circulation in advance of occlusion or unanswered myocardial oxygen demand.

Group 1.—The rules which apply to all men past the age of 20 years and to women with diabetes or hypertension are as follows: 1. All intrinsic factors that increase the heart's work load are corrected. This is especially true of weight, and we insist that patients be underweight. 2. We assuage patients' fears by pointing out that, in fact, we doctors and all their friends are also members of the arteriosclerotic-coronary "team," and, in the honest belief that this is true for most of these patients, we tell them that they are capable of attaining an age of 90 years, despite angina or infarction. 3. We discuss with patients the problems of coronary arteriosclerosis in common-sense fashion, to give them a realistic understanding, and we explain to them the concept of collateral blood circulation and how it will build up, given time. They are told that, although we do not know the specific factor necessary to stimulate collateral blood vessel growth, our experience indicates that collateral circulation will grow in advance of heart demand for practically any activity, provided the following three simple common sense rules are observed.

First, patients must act their age, in the sense that a ball player aged 35 cannot run as well as one aged 25, even though we doctors cannot detect a significant difference.

Second, patients must get into condition before attempting any new activity. Neglect of this rule explains why so many of them die of heart attacks while shoveling snow or hunting—they did not condition themselves for either of these pursuits. The young baseball pitcher gradually increases his activities each spring, first engaging in a few pitches, then one inning, and next several innings, before he attempts a full game. Our patients would not have thrown an arm away when they were young, and yet, unconditioned at the age of 50 years, they throw their heart away when it is not ready for the strain imposed by certain activities. There is a second important point about conditioning. To be in condition for one thing is not necessarily to be in condition for another. An athlete in perfect condition to run 100 yd. is not in condition to swim 100 yd. rapidly. This reminds us of the story of a patient who had a myocardial infarct. His work demanded climbing a flight of steps eight times a day. We had trained him for this activity over a period of months, making him walk first a few steps, then one flight of stairs, next two, and so forth. He returned to work and did well for 18 months, when he had another attack of angina. He said he got it polishing the rail while climbing the steps. We censored him. "We trained you to climb steps, not to polish rails. If you want to polish rails, let us know and we'll train you for that."

Third, and most important, is the common-sense advice to avoid physical or mental fatigue. Our contemporary pattern of fatigue, topped by an unusual degree of mental or physical strain, is taking its toll, no doubt. Nevertheless, one may wonder whether we are not deceiving ourselves. We often have seen executives who were harassed and overworked before they had a myocardial infarction but who became better executives after the infarction when they "put their feet up on the desk" and became "thinkers." Their fire ball gone, they "fool" their business problems with curves. The sad thing is that they need not have lost that fast ball in the first place.

Group 2.—In addition to the above, patients with a minor deficiency of heart circulation which is revealed only by exercise tests are cautioned to stay away from unconditioned, strenuous activity for several months but to lead an otherwise normal life.

Group 3.—This group of patients with severe coronary and collateral deficiency and angina pectoris demands our most careful attention. We must correct even the slightest deficiencies of the intrinsic factors that increase the work load of the heart, such as anemia, overweight, and others, and we must recognize and treat congestive heart failure early, because, *in our experience, the heart in failure* cannot rebound without help. A myocardium that does not put out an adequate supply of blood to the coronaries may be just as important a factor in angina as aortic stenosis which blocks the flow.

The moment a patient has angina he has an oxygen deficiency that injures his heart muscle, and if he injures the muscle often enough it will be replaced by scar tissue. To this group we apply the fourth rule of common sense—avoid attacks of angina at all costs. It is just common sense to know that if one can get angina by walking fast and avoid it by walking slowly, it would be wise to accept God's warning and walk slowly; or if angina comes with large meals, to eat small meals; or if it comes with walking up steps, to use the elevator.

At this point, special attention is given to the instruction of the patient who has had angina pectoris. He is worried and has focused on the multiple, small chest pains that everyone has had since childhood. We teach him how to recognize the pain that counts, the one that constitutes angina. Of greatest help in recognition is the duration of pain. "Does it last 30 seconds?" We keep time as the patient imagines the duration of his pains. Thirty seconds is a long time. Most of the nonsignificant "stitches in the chest" last but a few seconds.

We never give patients nitroglycerine at this stage of treatment. These patients, provided they do not fall into one of the four categories to be mentioned below, are allowed a trial period of one week to change their pattern of living in an attempt to prevent angina. If these patients can avoid attacks of angina, they will be able to increase their activities in time, as they become conditioned and as collateral blood vessels develop.

If, by following these rules, the patient is able to avoid angina, he is allowed to progress slowly back toward normal activity, always ready to draw back, however, if attacks of angina recur. At this time he is given nitroglycerine as a "spare tire" but is never allowed to abuse this privilege; he takes it if pain occurs or he takes it prophylactically if he cannot avoid breaking the therapeutic rules.

There are four types of angina pectoris, all serious evidences of an inadequate collateral circulation, that require more stringent treatment than the above: (1) angina that is not controlled by the above regimen, (2) an increase in the frequency of angina pains, (3) any one angina attack that lasts longer than 20 minutes, and (4) angina at rest. The latter is a late stage of this disease. The heart circulation in these patients is not adequate even when they are resting.

These four types of angina are the predecessors of myocardial infarction. These patients are treated just as if they had an infarct, in an attempt to establish collateral circulation and prevent infarction, with three weeks of bed rest after their last *pain, anticoagulants, and other measures—i. e., just* as the fourth group of patients with a recent infarct.

During the first week of this three-week period we adhere to every measure which lessens the load of the heart, such as quiet, sedation, no visitors, a

500-calorie diet, no strains or movements, including bowel movements, feeding by nurses, and so forth. We do not hesitate to use an oxygen tent for patient restraint as well as for inhalation therapy. Patients are told that this is akin to the spare tire on their car and that it is a part of our mutual game of the moment, i. e., "playing all our cards close to the chest."

The avoidance of bowel movements is an example of the meticulous attention paid to any unnecessary increase of the heart's work during this treacherous stage. The evolution of the method is worth comment. Some 12 years ago, concerned by the frequency of tragedies induced in these patients through bowel movements, we investigated the physiology of bedpan deaths.[8] This was followed by several years of fruitless endeavor to develop a practical method to negate the severe strains of the bear-down Valsalva maneuver. We did evolve an effective method of sorts, i. e., keeping the glottis open and breathing out during the period of straining. Practice of this method, however, resulted in far more physiological upset than occurred with the most difficult bowel movement. We remained at a loss as to how to gauge strain until about 10 years ago, when, after use of a commode by one patient had led to tragedy, we asked ourselves the question we should have asked in the beginning of the study: "Are bowel movements really necessary at this time?" In most cases they are not.

We have more than 200 patients who have gone through the first 12 days after acute myocardial infarction without a bowel movement. A 500-calorie, low-residue diet leaves but little to move; administration of a small amount (10-15 cc.) of mineral oil each night prevents fecal impaction. One patient in whom resumption had been overlooked requested permission on the 21st day for a bowel movement. In response to our surprised questioning he stated, "Doctor, my bowels only move at your command." Failure to prevent a first bowel movement sometimes occurs in the recently engorged patient. Complete failure of obstipation is found frequently in those elderly women who are addicted to taking cathartics and enemas; they consider a missed bowel movement a greater sin than missing church and will have no truck with these silly, new-fangled ideas.

About the second week, or three days after the temperature is normal in patients with infarcts, we start a graded increase in activity whereby, at the end of the third week, patients are allowed to sit up in a chair for one hour, three times a day. By the middle of the fourth week they are up and about the room. They are discharged as soon as they are able to go through the same daily routine in the hospital that they will have to engage in at home. Then, they are subjected to about one week of a graded increase of activity on the same floor level, followed by a trial climb of one flight of steps per day, short walks in good weather, and short rides in an automobile when someone else is driving.

These patients usually are ready for an office visit six weeks after the beginning of hospitalization. The basic rules are always stressed: act your age, get into condition before you attempt any new activity, and avoid fatigue. About seven weeks after hospitalization they are ready for job training. The work circumstances are analyzed, and the patient is conditioned for each one, such as walking up a hill to get to the bus, climbing steps, or lifting objects. When we feel that patients can perform their duties on this simulated basis they are allowed to return to work, first for a few hours in the morning, then for a full morning, next for a full day after a week-end, and so forth until they are working full time. As might be expected, the greatest difficulty, particularly with regard to fatigue, comes at the end of the work week.

In our experience, a patient with angina severe enough to necessitate hospitalization needs more careful supervision than one who has had an infarct and in whom scar tissue has replaced heart muscle. This is logical, since the oxygen demands of viable myocardium are greater than those of scar tissue.

There is an important philosophy that must be imparted to patients at this stage, namely, that a man is not happy unless he can do his job and that our only concern at this time is his job. Bowling, golf, and similar pursuits are frills with which we deal only later, when we are certain that a patient's heart circulation is adequate for performance of his job.

Throughout this course of rehabilitation the patient knows he may have to draw back to an earlier stage of activity if symptoms develop. This is particularly true of fatigue. We rarely see a patient who, observing our common-sense rules and with a recurrence of angina, has not had fatigue first. In other words, we believe fatigue is a symptom that occurs before the symptom of angina appears.

As time goes on we introduce the frills into these patients' lives in exactly the same manner as we prepared them for work. In golf, for example, they first hit practice shots, then play a hole or so on level ground on a fine day, and so forth.

Today, we are always confronted with the question about drugs and diets that may lower the blood cholesterol level. We do not use them. Patients who see the "cholesterol sword of Damocles" poised over every bite of food are miserable; our only instruction to patients, after weight reduction, is to eat high-protein and low-fat foods—"eat the meat, cut off the fat." Perhaps cholesterol and its allies are the predecessors of further "pipe rusting"; perhaps this may be prevented by soul-searing diets or expensive drugs; or perhaps not. This reminds us of the man whose doctor advised him that he would live to be 80 years of age if he abstained from smoking, drinking, and women. He died of shock on his 75th birthday immediately after finding out his doctor had been wrong. We assume the pipes are rusting, the same way the hair is graying and the wrinkles are wrinkling.[6] Our only concern is to grow an adequate supply of collateral blood vessels in advance of "rusting" by following the common-sense rules outlined above. This is what was done by a man who, despite occlusion of six major blood vessels at some time during his life, none of which ever bothered him, died of pneumonia at the age of 90 years.

Therapy with anticoagulants in ambulant patients is another method of promoting chronic invalidism. We reserve use of anticoagulants for the relatively few patients whose myocardium has been replaced by scar tissue to such a degree that cardiac failure is a constant threat. We believe the greatest value of anticoagulants lies in prevention of complicating thrombosis and infarction in other organs, such as the lungs. In general, we do not use the long-acting nitroglycerine-like compounds. We believe that angina pectoris, like the blinker lights at the railroad crossing, is a valuable warning of impending trouble.

Smoking is forbidden during the treacherous days before angina or infarction has been brought under medical control. Subsequently it is cautioned against but allowed. We have observed only two patients in whom smoking was a precipitating factor in producing an attack of angina. Patients are allowed to drink, they are urged to take routine vacations that are really vacations instead of energy users, and they may have relations with their wives. No wonder they like us and follow our suggestions.

Results

Is this method of treatment infallible for everybody? Of course it is not. There is a hard core of disbelievers who, once they feel well and do not have pain, will extend themselves, will gain weight, and will get into trouble. They want pills, not common sense. The percentage of disbelievers will be in direct proportion to the skill of the physician as salesman and practitioner of the art of medicine —his ability to show kindness toward and a sincere interest in his patients. There is a second group of patients who, for financial reasons, short-circuit the approach suggested by us. In both groups a second infarct or the recurrence of symptoms often converts a patient to a believer. There are patients who form a third group. Their heart muscle has been replaced by scar tissue due to an extensive infarction or repeated infarction. Their heart circulation is good, but they do not have the muscle to do the job. It is interesting, however, to note how very few patients cannot be returned to at least a comfortable existence.

The proof of any method of treatment is in the results. We have been using this common-sense approach for some 13 years. Our patients have returned to all types of work. One patient, first seen after his third infarct, has been working full time as an automobile mechanic for eight years without an episode of angina. His hobby is fishing of a relatively strenuous nature, namely, casting from a boat in the northern woods. He has completed his sixth annual vacation and is planning for his seventh. Others are driving trucks, lifting heavy objects, digging ditches, and climbing steps as insurance collectors in poorer districts where three flights for 50 cents is the usual work load.

We get repeated requests in the Memorial Heart Laboratory to study newer drugs for treatment of angina pectoris. We need this income, but our answer is always the same. "We do not have patients with angina who do not respond to this common-sense method of treatment, so why use drugs?"

As stated in the introduction, we are the diagnostic part of a heart surgery team. We respect the ability of these surgeons and the advances they have made possible in the field of heart disease, but we never have had a patient in whom an operation was considered necessary to control angina, to return him to a gainful occupation, or to enable him to live longer.

The patient response to our regimen is excellent. They like this approach: Their health is in their own hands. There is no magic. The dread outlook that used to accompany angina and infarction has been lifted. They are given simple rules that make sense—to act their age; to condition themselves for new activities; to avoid fatigue; and to avoid an attack of angina pectoris itself. As they first crawl, then walk, and next return to work and, finally, to the frills of life, such as dancing, golfing, and fishing, their confidence in themselves and in their physician grows. The role of the physician is now that of teacher and disciplinarian. This means careful instruction of patients and regular consultations, to either praise them for good performance or let them know the physician's displeasure when they stray from the rules. Our satisfaction is in relieving their worries and in guiding them to the acme of their capabilities, while retaining a margin of reserve for emergencies. "Not too warm, not too cold, but just right."

Summary

Studies by other investigators of the pathology and physiology of the circulation of the heart indicate that a narrowing of the cardiac arteries and an associated growth of collateral blood vessels is *an inherent process in practically all men past the* age of 20 years and in women with diabetes or hypertension. In some patients, functionally adequate collateral vessels develop to such a degree

that the narrowing or closure is of no clinical significance; in others, the rate of narrowing exceeds the rate of development of collateral vessels so that coronary insufficiency even to the point of infarction occurs.

Our experience indicates that functionally adequate collateral blood vessels grow in advance of significant narrowing, provided abnormal intrinsic factors that increase the work load of the heart and myocardial oxygen demand, such as obesity, anemia, hypertension, congestive failure, and others, are corrected, and provided patients follow three rules of common sense, i. e., to act their age, to get into condition before attempting any new activity, and to avoid unusual physical or mental fatigue. A fourth rule of common sense is applied to patients with angina pectoris, namely, that they avoid angina at all costs.

Patients who are not able to avoid angina or who have an increase in the frequency of angina, any one attack that lasts longer than 20 minutes, or night angina are hospitalized and treated as if they had a myocardial infarction. The growth of a functionally adequate collateral blood circulation in patients with angina pectoris or myocardial infarction is a product of months rather than days. Extreme care by the physician is mandatory to insure that the myocardial oxygen demand never exceeds the ability of the cardiac arteries to supply oxygen during this period. Relief of the symptom of angina, even of the so-called intractable type, has been accomplished in all patients who, treated over a period of 13 years, have adhered to this common-sense medical management.

Most of these patients have been returned to a full work status, regardless of occupation. Failure to return to previous work has been based on associated lesions, such as valvular heart disease or emphysema, and not because of an inadequate heart circulation.

Surgery has never been considered necessary to control symptoms, to prolong life, or to increase work capacity. It is apparent that patients do a better job growing their own collateral circulation than surgeons can ever hope to stimulate or implant. In general, drugs and diets that control blood cholesterol and lipid levels and drugs that lower the prothrombin time have not been found necessary.

Research attention should be focused on the basic methods whereby a collateral circulation develops and on methods of preventing narrowing or closure. Studies along these lines are in progress.

441 Vine St. (2) (Dr. Green).

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DETERMINISM OR FREE WILL?—Deceptive is the theory that all cause for human actions lies in definable conditions, thus all can be explained and justified, not condoning the evil things people sometimes do, but ascribing their destructive behavior to factors beyond their control. Better it is, it seems to me, for man to accept the more divine belief that he is responsible for himself, that purpose can be a substitute for aimlessness, that conditions can be overcome by the power of the human will, that self-indulgence and ego-centric motivations have never, in all history, served to satisfy the inner cravings of the human spirit. Rather, there is always the window to wash, if it be clouded; the sun to be met at dawn, rather than to be curtained by opaque animal comfort; rivers of experience to be forded despite the hazards of the flood.—C. F. Hansen, Ed.D., Mental Health Aspects of Desegregation, *Journal of the National Medical Association,* November, 1959.

J.A.M.A., Feb. 20, 1960

EVALUATION OF THE CARDIAC PATIENT FOR WORK CAPACITY

Joseph G. Benton, M.D., Ph.D., Brooklyn, N. Y.

The relative importance of physical activity and emotional stress among the occupational factors leading to heart disease has been difficult to determine from a review of published data. There is also a lack of reliable tests for evaluating the work capacity of cardiac patients. In order to assess the strain of a given job it is necessary to consider not only the average energy requirements but also the peak loads. Experience has shown, however, that workers who return to properly selected productive employment after recognition of their cardiac disability have at least as good a prognosis as those who do not return and that with respect to efficiency, regularity of attendance, freedom from accidents, and adaptability they compare favorably with other groups of workers.

It has been suggested that there has been an increase in the incidence of coronary artery disease in recent years. This disease of modern civilization has assumed prominence during a period in which heavy labor is less common and the length of work hours has decreased while other pressures have increased. Constitutional factors are important in coronary artery disease, but there is also some evidence of variation of its incidence with environment. In addition, its relationship to physical effort is highly controversial, with, in many instances, significant medicolegal connotations.

Special interest in the general area of physical activity related to coronary artery disease originally stemmed from experience with numerous patients undergoing rehabilitation whose hemiplegia was a complication of underlying systemic cardiovascular disease. These patients passed through a graduated program of retraining, including, among other procedures, activities of daily living and ambulation ranging from level walking to stair-climbing of varying intensity. While complete follow-up data for these patients are presently not available, only rarely did their cardiovascular status deteriorate clinically while they were under observation. In this connection, it should be emphasized that rehabilitation was not considered feasible in any patient in whose case (1) there had been such cerebral damage as to preclude adequate mentation to allow for recall of retraining techniques, (2) the malignant phase of arteriolar nephrosclerosis had supervened, or (3) intractable congestive heart failure or coronary insufficiency was present. Indeed, these were considered contraindications for patient selection.

Review of Literature

Review of the literature indicates that there are divergent opinions about the relationship of effort or stress to coronary thrombosis. One group believes that coronary thrombosis almost invariably occurs in the absence of effort, usually at night and often in the early morning hours, when the blood pressure is low and the coronary blood flow diminished. Some maintain that angina pectoris is almost always precipitated by stress, either physical or psychological, and that this is related to coronary insufficiency in roughly 50% of cases but is coincidental in the pathogenesis of coronary thrombosis.[1] Others believe that there is good evidence that sudden, exceptionally heavy physical exertion may be followed by coronary occlusion.[2] In addition, there are those who believe that acute psychological disturbances may have a direct bearing on coronary occlusion.[3] All are agreed, however, that preexisting intrinsic coronary artery disease must be present.

With reference to psychosomatic factors in the pathogenesis of this syndrome, it is of interest to note that there have been described[4] increased capillary permeability and hemorrhage, hemoconcentration, and hypertension or hypotension (depending on the intensity of the stress) during the alarm reaction of the "general adaptation syndrome." In addition it has been demonstrated that significant changes in hemodynamics and electrocardiographic patterns occur during psychiatric interviews relating to stressful life situations.[5] Exercise and emotional stress have also been shown to cause not only changes in blood pressure but also an increase in blood viscosity and hematocrit value and a decrease in sedimentation rate and coagulation and prothrombin times.[6] It would appear, therefore, that there is objective evidence of the influence of physical and emotional factors on the vascular tone and the clotting mechanisms of the blood and that the central nervous and endocrine systems may be involved.

From the Department of Rehabilitation Medicine, College of Medicine, State University of New York, Downstate Medical Center, New York City.

Read in the Symposium on Current Concepts of Heart Disease and Employment before the Joint Meeting of the Section on Diseases of the Chest and the Section on Preventive Medicine at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

The suggested increase in coronary artery disease is not due simply to an increase in coronary atheromas. Other conditions are necessary, and the complex of atheroma, thrombosis, and the capacity of the heart to deal with these in relation to the demands made on it is an important consideration. Some information relative to this has appeared in the American literature, but the most extensive surveys in this connection have been made recently by the Social Medicine Research Unit of the Medical Research Council of Great Britain.[7] It was hoped that these studies would afford knowledge of coronary artery disease as a public health problem and also that possible social factors which may be favorable or unfavorable to its incidence might be delineated.

The occurrence of coronary artery disease in certain groups of weekly paid employees of the London Transport Executive during 1949 and 1950 was carefully studied in approximately 31,000 men aged 35 to 64. The experience of drivers and conductors of the "red" buses (double-decker), drivers and conductors of trains and trolley buses, and motormen and guards on the underground railways was observed. Analysis of the data suggested that coronary artery disease occurs differently in the drivers (sedentary) and in the conductors (active). Angina pectoris was relatively more common among the conductors, whereas rapidly fatal coronary thrombosis was more common among the drivers. Of the first episodes among the drivers 13% took the form of angina—or were so diagnosed—compared with 39% in the conductors. Contrariwise, the "immediate" deaths accounted for 31% in the drivers (25 "immediate" deaths in 80 cases) as against 19% in the conductors. The conductors therefore had less lethal coronary artery disease than the drivers, and the disease seemed to be appearing in them at a later age. What disease the conductors had was less severe, with a smaller early case fatality as well as a lower incidence and therefore a substantially lower early mortality. On the other hand, the conductors manifested more of the benign type of disease, in the form of angina pectoris, than the drivers. These observations were judged reliable, since there was a triple check on the diagnoses—by the men's own general practitioners, medical officers of the London Transport Executive, and, in addition, corroboration in over 90% of the cases through documented confirmation by a specialist or a hospital, or both. Most significant is that this was an epidemiologic study of the experience of different occupational groups. The population consisted of men from the same part of the country, served by the same health and welfare services and living in broadly similar social circumstances during the same period of time. Conditions of sickness absence and benefit were similar throughout for the population studied.

The differences in figures between drivers and conductors are considered significant ($p<0.001$) when statistically analyzed, and therefore they would appear not to be due to faulty data or small numbers. Possibilities for the observed variations are as follows: 1. There may be differences in constitution and early experience of the conductors and drivers, one expression of which is that the men select their different jobs for themselves. 2. While there may be mental strains in both driving and conducting, these may be of different kinds, and this difference may be a factor in the higher incidence and mortality among the drivers. 3. The greater physical activity of "conducting" on the double-decker vehicles may be a cause of the lower incidence and mortality in the conductors.

The latter seemed the most likely explanation, and the hypothesis was tested by making a similar two-year study of the mortality and morbidity statistics referable to coronary artery disease in 110,000 men, 35 to 59 years of age, who were postal workers and civil servants and whose work involved three major categories of physical activity.

The results showed that the total incidence of coronary artery disease is lower in postmen (active) than in the sedentary workers. Their case fatality was also lower: one-third in the postmen (57 of 171), compared with almost one-half in telephonists, executives, and clerks (70 of 143). Again, as with the transport workers the early mortality of the physically active group (0.6 per 1,000) was substantially less than that of the physically inactive (1.2 per 1,000). On the other hand, the incidence of angina was higher in the postmen than in the sedentary workers (0.7 as against 0.5 per 1,000). The grades of postal employees which are "intermediate" with respect to physical activity showed total incidence and early mortality that lay, on the whole, between those of the postmen and the sedentary workers.

The experience of the postal workers and the civil servants may therefore be said to resemble that of the transport workers: The physically active group (the postmen) have less coronary artery disease, and what disease they have is less severe. It would thus appear that the data strongly suggest that physical activity at work is important in relation to the incidence of coronary artery disease in middle-aged men.

Further confirmation of this premise was afforded by an analysis of the mortality due to coronary artery disease related to strenuousness of work in the total male working population aged 45 to 54 in England and Wales from 1930 to 1932. Briefly, the mortality from coronary artery disease of the groups doing physically heavy work was less than one-half that of the light workers. If there is a major psychological factor operating to produce the mortality gradient already noted, the scatter of the sample suggests that it is so intimately associated with the physical factor as not to be readily distinguishable from it. The early observations of 1930-1932 were corroborated by analyses of records of men aged 45 to 74 dying of coronary artery disease in London and the home counties in March, 1952. This would tend to obviate the technical question of possible variations in diagnoses.

Of special interest, and in some respects contradictory to the previous general conclusions about the relationship of type of work and coronary artery disease, are data on physicians. A study[8] was made of over 6,000 male medical practitioners in Britain, aged 35 to 64, who held "immediate" noncancelable sickness insurance. The incidence of first attacks of coronary artery disease from 1947 to 1950 was twice as high among the full-time general practitioners aged 40 to 64 as it was in full-time consultants or specialists and public health officials. When "G-P specialists" were added to the full-time general practitioners, the incidence in the composite group was 1.8 times that in the remainder. Finally, the incidence of coronary artery disease in a large group of nonmedical men of comparable age in the civil services, the professions, and industry was well below that of the full-time general practitioners and resembled that of the other physicians. A comparison with the provisional mortality from coronary disease among the men of comparable ages of England and Wales in 1950 gave similar results. Comparable data have been presented in studies done in this country in 1947-1948.[9] It is possible that the well-known day-to-day stress, other than physical, under which the average general practitioner operates, may be a causative factor for the increased mortality in this group. Such factors, not the least of which may be psychological, would admittedly be difficult to quantitate.

Reasons for these significant facts are not immediately apparent, but there is little doubt that further studies relating to coronary artery disease and physical and psychological factors, the effect of physical activity on coronary circulation, other occupational and social factors, nutritional factors (including obesity), and constitutional factors are clearly indicated.

In the United States, while such complete studies are not available, a survey of death rates by occupation performed in the predepression era (based on data of the United States census of 1930) revealed that farmers and agricultural workers, as a group, had the lowest mortality, followed next in incidence by the executive socioeconomic group. Confirmation of this for the executive group was afforded by a report of the joint committee on mortality presented in the 1949 *Transactions of the Society of Actuaries,* which indicated that the executive group (those carrying large life-insurance policies) did not have an increased mortality as compared to persons insured for small amounts. Such evidence should be borne in mind in evaluating a statement appearing in a *Fortune* magazine article—"The number of executives nipped in mid-career seems to be rising, and the frequency with which 'heart failure' is cited gives this the status of an occupational disease"—as well as when reading obituaries of prominent industrial figures in the morning newspapers.

Work Capacity Evaluation Methods

While there are many groups throughout the country actively interested in the evaluation of cardiac patients for work, there is, as yet, no single definitive test which would assess the work capacity of such patients. In general, it can be safely stated that the demands of stresses of work on the individual person accrue from the physical and emotional demands of work plus the stress imposed by the environmental conditions under which the work is performed. The physical, emotional, and environmental stresses are additive, and real progress has been made by work physiologists in several countries in the areas of physical and environmental influences; however, it is not yet known how to quantify emotional stress.

The physical demands can be roughly estimated by measuring the reaction of a person to a specific job. Cardiac rate, blood pressure, respiratory rate, oxygen consumption, blood lactic acid level, body temperature, and electrocardiographic changes during work and recovery have been measured but some question has been raised as to the validity of such measurements for estimating work capacity.

In general, it can be stated that, other variables being equal, the compensated cardiac patient does not significantly vary from the normal subject, providing his cardiac reserve is not exceeded. It should be of interest to note that in American industry today most workers are expending energy at a rate of 3 to 4 calories per minute, or fewer, with the notable exceptions of foundry workers, longshoremen, and lumberjacks. This is an extremely low level of energy expenditure and is far below that used in various recreational activities, including walking.

A recent tool which has been utilized in such studies is the Lauru force plate. This device measures the physical demands of work which may be below those causing changes in oxygen consumption above the resting level. Cardiac catheterization has also been utilized to measure differences in blood pressure, blood flow, and cardiac work in response to certain levels of physical work, emotional stress, and environmental stress in laboratory studies. This method is quite sophisticated, however, and does not lend itself to making measurements "on the job."

The demands of work can be estimated without making any direct measurements on the individual patient. The metabolic cost of all component movements that make up a job can be summated, and the amount of work done can be calculated in terms of foot-pounds or kilogram-meters. With use of a variety of physiological techniques, numerous studies in many countries have been reported indicating energy-requirement figures for a multitude of jobs. At first these were for normal subjects but recently data have been evolved for the patient with cardiac disease as well. It should be borne in mind that the value of such data should not be overstressed, since neither psychogenic factors nor the rate and conditions of work apparently enter into consideration. In addition, the individual patient's attitude toward work is extremely difficult to quantitate.

From the laboratory other groups have gone directly to the job situation and, with a wide variety of extremely sophisticated newer electronic metering devices, have been able to study the patient actually at work. In conjunction with such highly refined methods, careful cardiologic examination and social and job analyses have been used in the ever-increasing numbers of work classification units that have been established in many communities throughout the United States. Studies have indicated that assessment must consider not only average energy requirements but also peak loads. Generally speaking, most intolerable jobs are such because of the peak loads, whether they last for only a few minutes or a half-hour. Most workers in American industry coast along at low energy-expenditure levels for the bulk of every day. In addition to the direct energy costs of the job, it is also necessary to be aware of many aspects of the patient's life, such as the pace at which he works, his attitude, and the attitudes of those with whom he works. Furthermore, consideration must also be given to his home and marital life and problems relating to transportation to and from the job.

The use of certain laboratory tests, in an attempt to derive a satisfactory test for cardiac function, while indicating certain differences between cardiac patients and noncardiac subjects, has not been a satisfactory technique for measuring the response of the patient to actual on-the-job conditions. Numerical fitness indexes, while adding greatly to knowledge of cardiovascular dynamics, have not been accepted as yardsticks for job placement, especially at low energy-expenditure levels. Preexercise ballistocardiograms also were found not to be of value in this connection.

There is ample evidence to date that, with proper job placement and satisfactory mental and emotional states, the prognosis of the worker with cardiac disease who returns to productive employment is equal to, or better than, that of the worker who ceases work immediately on diagnosis or recognition of his cardiac disability. Long term follow-up studies made in a number of industries have revealed a favorable experience regarding efficiency, absenteeism, accidents, and the need for special job modifications.

Summary

It would appear that, except for the general medical practitioner, the old adage, "Hard work never killed anybody," seems to have some objective basis in fact. Patients with cardiac disease, when selectively placed in industry, can perform creditably.

450 Clarkson Ave. (3).

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EMBOLECTOMY IN ARTERIES TO EXTREMITIES

Lester Blum, M.D.
and
Irving Rosenthal, M.D., New York

Forty-eight embolectomies were performed in 38 patients selected for operation by the authors, depending largely on the status of epicritic sensation in the affected extremities. Little diagnostic or therapeutic help was obtained from sympathetic block procedures. Where epicritic sensation was normal or absent only in the metacarpus or metatarsus, a conservative regimen was followed. The operative procedure always included a complete flushing out of all clotted material from the distal arterial tree. Of 43 extremities saved out of the 53 extremities in jeopardy, half were arteriosclerotic and half rheumatic; of the 10 extremities lost, 7 were arteriosclerotic. The arteriosclerotic group of patients had more extensive disease, were older, and were generally in poorer condition than the rheumatic group.

Prior to the last decade, embolectomy was considered something of a surgical adventure. Despite the pioneer work of the Swedish school, the procedure frequently was performed only on recognition that conservative treatment had failed.[1] Therefore it is not surprising that an unhappy result was accepted philosophically. Another deterrent was the popularity of treatment with papaverine, the various sympathetic block techniques, and the anticoagulants. Since the general condition of patients suffering from arterial emboli is usually poor and the underlying heart disease chronic in nature, the adherence to a conservative attitude is quite understandable. Consequently much of the pertinent literature consisted of isolated reports of successful operations.

In the last decade, the remarkable technical improvements of vascular surgery have changed all this so that embolectomy, when timely, has become a procedure in which success is to be expected and failure explained. Because of the inherent mortality of this group of systemically sick patients, the operative results should be gauged in terms of extremities saved as a direct result of intervention.

We wish to present our personal experience with 48 consecutive embolectomies. Because of our intimate concern with each case we feel that the indications for operation, the intervals between occlusion and operation, the technical problems, and the clinical results can be surveyed with an accuracy not possible in an analysis of alien, charted material.

Indication for Embolectomy

Obviously, the basis of any treatment is the establishment of a diagnosis. The physical signs of acute arterial occlusion in an extremity are too well known to need repetition. The association of arrhythmia and an evident block at an arterial bifurcation constitutes an unmistakable picture. Only one of our patients was eurhythmic, and in only one instance was an error committed in localization of the embolic site.

Only those cases in which the ischemia was constant or progressive under careful observation were selected for operation. The crux of the decision is the status of epicritic sensation in the affected extremity. It has been our experience that complete tissue survival is certain if epicritic sensation remains unimpaired. The recognition by the patient of light touch and pinprick confirms the presence of sufficient oxygen tension in the distal capillaries to maintain the functional integrity of the peripheral nerves. Since nerve cells are more sensitive to oxygen deficiency than those of any other tissue, their continued function warrants the assumption of a satisfactory gas exchange throughout the affected part. There is no laboratory test for the mensuration of blood flow that remotely approaches the specificity of this physical sign. It approaches the infallible in that we have never seen tissue death in the presence of unimpaired epicritic sensation.

The color of the affected part and its temperature are of merely ancillary value in estimation of the collateral response after arterial occlusion. These latter physical signs are influenced by numerous factors, including the personal judgment of the observer. Furthermore, it is well known that marked pallor and coolness are common in the hands and feet of normal people with perfectly adequate blood flow.

The level of epicritic sensation must be carefully ascertained and watched during the short period of intensive observation. Any increase in sensory loss or the persistence of anesthesia of the foot or hand strongly indicates operative intervention, whatever the color or temperature.

Motor activity is of rather dubious value in estimation of ischemia and, in fact, can be quite misleading. This is equally true of muscle-tendon-joint

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From the surgical services of the Mount Sinai Hospital and the Beekman Downtown Hospital.

deep sensation. In fact, in the early stages of peripheral gangrene, toes and fingers can be actively moved.

In short, embolectomy should be performed because of the likelihood of tissue necrosis or severe, crippling functional loss. In no instance of normal epicritic sensation was operation undertaken.

We are puzzled by statements to the effect that it is difficult to recognize and localize peripheral arterial emboli.[2] With the possible exception of oscillometry, any type of instrumentation is quite superfluous.

In view of the better collateral response characteristic of the superior extremity, it is not surprising that in this consecutive series there were only 3 brachial embolectomies as against 45 in the lower extremity.

One facet of our experience is worthy of mention, since it is quite at variance with the prevailing opinion. We derived little prognostic or therapeutic help from the use of sympathetic block procedures such as the paravertebral injection of procaine into the lumbar region or the infiltration of the stellate ganglion. On the contrary, it is our opinion that valuable time is wasted and that extremities unnecessarily are placed in jeopardy by almost routine, repetitive performance of these procedures.

Finally, many of these patients are in poor condition and all are chronically ill. The general state of their health is not considered a contraindication to necessary embolectomy. In this group a gangrenous extremity is an invariably fatal complication.

Timing of Operation

It is evident that the shorter the time lapse between lodgment of the embolus and restoration of the circulation, the better the result. The old concept of the six-hour or eight-hour deadline should be abandoned. It appears to be based on collective data.[3] We were able to save one extremity, although with permanent drop foot and some loss of muscle tissue, despite a lapse of 26 hours between occlusion and clearance of the arterial tree. Similar reports appear in the literature.[4]

In our series the mean time interval in cases with extremity survival is 12.1 hours±1.6; that for extremities lost is 14.1 hours±2.9. Since the standard deviation of the difference is 3.4, it follows that no statistical significance attaches to the difference in time interval between the good and poor results in this particular series. In short, the majority of patients presented themselves within a reasonable time. This offers the analytic advantage of allowing recognition of those other factors which usually assume secondary importance when wide variations in time interval dominate the picture.

Although operation should not be denied up to 24 hours, it is doubtful that complete success is attainable thereafter. In one of our patients, embolectomy 24 hours after occlusion resulted in the restoration of peripheral pulses and a warm foot of good color. However, progressive, aseptic, ischemic muscle necrosis led to thigh amputation 10 weeks later.

Operative Technique

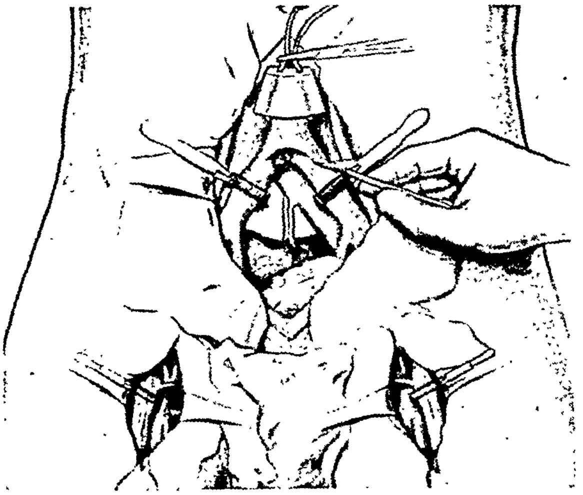
The term "embolectomy" is applied to the procedure of clearing embolic and thrombotic material from the arterial tree of an extremity, regardless of the number of necessary arteriotomies. The affected extremity is completely prepared and draped off, including the digits. In the arm, this includes the axilla, neck, and hemithorax. In the lower extremity, the abdomen is included up to the costal margin for one side and to the nipples in the event of an aortic embolus. This permits examination of the distal portions of the extremities so that the operator himself can palpate for peripheral pulses without unsterilizing the field.

It is preferable to remove aortic emboli by laparotomy and direct aortotomy. This method was used by Bauer[5] in 1913 in the first successful removal of an aortic embolus. A variation of this approach has been described by Linton,[6] who incises the right common iliac artery and milks the clot out while occluding the aorta and the other iliac vessels with modified Bethune tourniquets. Murray[7] has advocated use of the retroperitoneal abdominal approach and incision of the right common iliac artery.

Since the condition of patients suffering from lodgment of an embolus at the aortic bifurcation frequently is poor, an indirect approach has much logical appeal. Credit for the first use of catheters, suction, and irrigation in the dislodgment of emboli through distally placed arteriotomies must go to Handley,[8] who, in 1907, failed to completely remove an iliac embolus with propagated clot, despite a valiant effort. In his desire to do a complete arterial toilet, he opened the popliteal artery as well and passed through it fine catheters in an attempt to clear the channel well down the extremity. We feel that the proximal passage of instruments through femoral or iliac arteriotomies in an attempt to clear the aortic bifurcation is not a wise move nor usually an effective one. The danger of pushing thrombotic material into the blood stream of the opposite extremity is real.

In our operative plan, the femoral arteries are first exposed and serrefines applied to prevent material being swept down (see figure). Then laparotomy is performed, the retroperitoneum exposed, and the aortic bifurcation isolated by passage of rubber catheters above as well as below the iliac vessels. With the blood flow thus controlled, a curved incision is made in the concavity of the bifurcation.[9] Through this opening almost all the clotted material can be removed easily. After suture of the aortotomy wound, the taut catheters are released and the blood stream thus is released. Short transverse arteriotomies then are made cephalad to the femoral serrefines. This allows flushing out of smaller particles. After these transverse arteriotomies are sutured all clamps are removed, the abdomen is closed, and the extremities are carefully examined on the table. If there is any doubt as to the completeness of the procedure, the patient is turned and the popliteal artery on that side is exposed. If pulsating toward and including its division, the wound of exposure promptly is closed; if not, a transverse incision is made in the popliteal artery and blood flow established.

Since femoral and iliac emboli constitute the majority of cases, the operative procedure easily can be formalized into a fairly constant technical ritual. The initial step is exposure of the common femoral artery and its divisions, the deep and superficial femoral vessels. If the embolus is lodged at this site, a short transverse opening in the common femoral artery just at the origin of the two divisions is made so that the distal clot can be irrigated and sucked from both the superficial and deep femoral vessels. After this the embolus can be gently extracted and the arteriotomy wound closed. In the case of an iliac embolus, the inguinal ligament is divided and the exposure cleared cephalad to the necessary level. If essential, further transverse arteriotomies can be made. With the restoration of a good pulsation at the femoral level, the operation is completed only by making certain that there is no distal occlusion.



Exposure of femoral arteries and application of serrefines before exposure of aorta for removal of embolus at bifurcation.

In the absence of indisputable pedal pulses, it is our routine to turn the patient over and expose the popliteal artery. If this vessel is not actively pulsating, the procedure must be carried on until it is.

We do not advocate opening the posterior tibial artery at the ankle.[10] In addition to the disadvantage of so distal an incision in an extremity subjected to severe vascular insult, we have not experienced tissue loss in the presence of an actively pulsating popliteal artery down to, and including, its division into the tibial vessels.

There are three technical points in the performance of embolectomy which are worthy of emphasis: 1. Arteriotomies should be placed transversely. This is of great help in diseased vessels, since it permits easier exposure than the commonly employed sagittal incision and can be closed more readily. Furthermore, there is little constriction of the lumen. 2. Completeness of the arterial toilet means the difference between success and failure. It is essential to flush out all clotted material as far down the extremity as possible. This may prove tedious but it is basic. 3. The procedure of embolectomy in an extremity is not properly concluded unless the pedal pulses are unequivocally present or the exposed popliteal artery is pulsating down to, and including, its bifurcation.

Clinical Data

Our personal experience is composed of the 48 consecutive embolectomies about which data are presented in table 1. Since 5 of the emboli were aortic, 53 extremities were in jeopardy. Of these, 10 were lost, 5 through amputation and 5 through ischemia at the death of the patient. There were 14 iliac emboli, 18 femoral, 8 popliteal, and 3 brachial. This distribution (tables 1 and 2) resembles that reported by others.[11]

The paucity of upper extremity procedures is not surprising, since this is a less common site for lodgment and surgery is required less often because of the remarkable recuperative power of this extremity after vascular occlusion, in sharp contrast to the inferior limb. This can be ascribed to the profusion of collateral blood vessels about the elbow, to the lesser blood flow demand of the smaller muscle mass of the arm, and to the relative freedom of the upper extremity vasculature from arteriosclerosis. In fact, we performed embolectomy in the arm only after prolonged observation and an established certainty that matters were not responding to a conservative regimen. In one case, brachial exploration was undertaken after 50 hours of observation and with a good result.

The 48 operations were carried out on 38 patients; 17 of the patients died postoperatively. This approximates the usually reported mortality of 50% in this category of patient. The chief cause of death was heart failure, with cerebral embolism second and shock third (table 2). Since these patients are desperately sick, the success of the procedure should be measured in terms of extremities saved that otherwise would be unequivocally lost.

It is difficult to understand how authors can compare the operative and conservative methods of treating peripheral embolism in terms of mortality and extremity salvage. In the first place, the patient deaths are not related *ipso facto* to the performance of the operation. Second, if patients are carefully selected for exploration on the basis set forth above, the results of conservative care must necessarily be better than in the operative group, since the latter includes only those patients definitely in danger of losing limb and, possibly, life.

Since the interval between lodgment of the embolus and restoration of blood flow was not significantly different in patients with good and bad results in our series, and since the identical technique was followed throughout, it is possible to evaluate the factor of pathogenesis (table 1). Of 43 extremities saved, half were arteriosclerotic and the other half rheumatic. However, of the 10 extremities lost, 7 were arteriosclerotic. Not only are these patients older and in poorer condition than those in the rheumatic group, but in them the arterial tree is extensively diseased. As mentioned previously, this

TABLE 1.—*Results of Forty-eight Consecutive Embolectomies in Thirty-eight Patients*

Patient, No.	Age, Yr.	Site	Time Lapse Between Lodgment and Removal of Embolus, Hr.	Pathogenesis	Results	Remarks
1	58	Aortic	9	Rheumatic	Good, l. Good, r.	Postoperative fecal fistula; died 7th day, congestive heart failure
2	48	Aortic	4	Rheumatic	Good, l. Good, r.	Discharged after 56 days
3	56	Aortic	6	Rheumatic	Good, l. Good, r.	Died within 48 hr., congestive heart failure
4	52	Aortic	6	Rheumatic	Good, l. Good, r.	Occurred 9 days after commissurotomy
5	38	Aortic	6	Rheumatic	Good, l. Good, r.	Discharged after 11 days
6	57	Iliac	9	Arteriosclerotic	Good	Discharged after 33 days
7	36	Iliac, l. Iliac, r.	5	Rheumatic	Bad Bad	11th day left thigh amputation; right leg ischemic; died after 32 days, cerebral embolus
8	57	Iliac, l. Iliac, r.	9	Rheumatic	Good Good	Died in operating room in shock; post mortem examination showed patent arteries
9	46	Iliac, l. Popliteal, r.	25	Rheumatic	Bad Good	11th day left thigh amputation; frequent subsequent mitral valvulotomy
10	70	Iliac, r. Femoral, l. Femoral, l. (8 days later)	5	Arteriosclerotic	Good Good Good	Died within 29 days postoperatively, septicemia; also had visceral emboli
11	55	Iliac	6	Arteriosclerotic	Good	Discharged after 24 days; well 2 yr. later
12	53	Iliac, l. Iliac, r.	10	Arteriosclerotic	Good Bad	Sudden death in wheel chair, 4th day
13	52	Iliac, l. Popliteal, r.	9	Arteriosclerotic	Good Good	Sudden death 3rd day, coronary thrombosis
14	70	Iliac, l. Iliac, r.	12	Arteriosclerotic	Good Bad	Died in shock, 10 hr. postoperatively, aortoiliac thrombosis
15	80	Iliac	16	Arteriosclerotic	Good	Sudden death within 24 hr.
16	38	Femoral, l. Femoral, r.	7	Rheumatic	Good Good	Died, 18 days postoperatively, cerebral embolus
17	51	Femoral	8	Rheumatic	Good	Died in operating room, cerebral embolus
18	76	Femoral	8	Arteriosclerotic	Bad	Died within 10 days, congestive heart failure
19	48	Femoral	7	Rheumatic	Good	Subsequent mitral disease
20	40	Femoral	20	Rheumatic	Good	Discharged within 48 days
21	67	Femoral, l. Femoral, r.	25	Arteriosclerotic	Bad Good	Left leg amputation, 6 days postoperatively; died within 7 hr.
22	63	Femoral	6	Arteriosclerotic	Good	Discharged after 32 days
23	60	Femoral	12	Arteriosclerotic	Good	Discharged after 18 days
24	71	Femoral	17	Arteriosclerotic	Good	Sudden death within 14 hr.
25	44	Femoral	5	Rheumatic	Good	Discharged after 11 days; slight drop foot
26	61	Femoral	30	Arteriosclerotic	Bad	Pulses restored but muscle necrosis necessitated amputation, 10 wk. postoperatively
27	60	Femoral	6	Arteriosclerotic	Good	Discharged after 21 days; well 1 yr. later
28	60	Femoral	3	Neoplastic	Good	Discharged after 14 days; died after 2 mo., lung cancer
29	61	Femoral	16	Arteriosclerotic	Good	Well 1 mo. later
30	63	Popliteal	24	Arteriosclerotic	Good	Discharged after 27 days
31	73	Popliteal	8	Arteriosclerotic	Bad	Thigh amputation; discharged after 24 days
32	69	Popliteal	12	Arteriosclerotic	Good	Died 2nd day, pulmonary embolus
33	69	Popliteal	17	Arteriosclerotic	Good	Died 8th day, coronary thrombosis
34	39	Popliteal	15	Rheumatic	Good	Subsequent mitral disease
35	63	Popliteal	3	Arteriosclerotic	Good	Discharged after 12 days
36	72	Brachial	50	Arteriosclerotic	Good	Discharged after 9 days
37	74	Brachial	12	Arteriosclerotic	Bad	Died 4th day, congestive heart failure; diabetes, severe
38	44	Brachial	10	Rheumatic	Good	Subsequent mitral disease

Of the 48 emboli, 45 presumably originated in the heart, one apparently arose from an aortic atheromatous ulcer, one was a clot from the wall of an aortic aneurysm in process of resection, and one was a neoplastic embolus coming from a carcinomatous lung (table 2).

poses a problem in the mechanics of arteriotomy, vessel exploration, and closure. It is difficult to clear a tenacious clot from tortuous, irregularly narrowed arteries. The final result is threatened also by the greatly diminished collateral potential of the diseased smaller vessels.

Since there was reason to believe that a large number of our patients lacked pedal pulses before embolic occlusion occurred in their larger vessels, we could not establish the restoration of distal pulses as essential for a good result designation. We based our results solely on unequivocal preservation of a functioning extremity without tissue loss or any damage sufficient to cause overt signs of ischemia. In this connection, it should be noted that in one patient, operated on 24 hours after occlusion, peripheral pulses were restored and there was no loss of integument. However, after 10 weeks it was necessary to perform a thigh amputation because of progressive aseptic muscle necrosis resulting from the initial period of ischemia.

Table 2.—*Analysis of Forty-eight Consecutive Embolectomies in Thirty-eight Patients*

Type of Embolus	No.	Extremities in Jeopardy	No.
Aortic	5	Saved	43
Iliac	14	Lost	10
Femoral	18	Amputated	5
Popliteal	8	Ischemia (at death)	5
Brachial	3		
Origin of Embolus	**No.**	**Postoperative Deaths**	**No**
Heart	45	Heart failure	10
Aortic atheroma	1	Cerebral embolus	3
Aortic aneurysm	1	Shock	2
Lung neoplasm	1	Septicemia	1
		Pulmonary embolus	1

Analysis of Bad Results

As previously noted, there was no significant difference between the group of 43 salvaged extremities and the 10 bad results with regard to elapsed time between lodgment of the embolus and restoration of blood flow. The average ages of both groups also were identical (table 1).

The only significant contrast was in pathogenesis. Only 3 of the 10 lost extremities occurred in patients with rheumatic disease. Furthermore, technically two of these were not handled as well as the remainder and the third followed a time interval of 25 hours and an incomplete procedure. The remaining seven bad results were all arteriosclerotic in origin. This is in sharp contrast to the equal incidence of rheumatic and arteriosclerotic disease in the salvaged group (table 1).

It is quite possible that the systemic and local factors accounting for this loss of limb will always remain insurmountable. The disseminated nature of atheromatous disease throughout the vasculature of the extremity and the precarious state of the tissues preceding the added insult of embolization are weighty factors in the balance against success. Even the mechanical restoration of blood flow in diseased major arteries is made difficult by filling of the irregularly constricted passages by tenacious clot.

Incision, exploration, and arteriotomy closure of a diseased vessel can become a complicated, tedious affair, threatening successful completion of an embolectomy. The intima strips, the media fragments, and the sutures do not hold, because the brittle vessel wall is cut through by the silk thread. There can be little doubt that, next to the time interval, the condition of the peripheral vasculature is the most important single factor in determining the success of embolectomy.

Summary

Forty-eight consecutive embolectomies performed by us were subjected to analysis. Aside from the time interval between lodgment of the embolus and reestablishment of blood flow, the most significant factor determining success was the condition of the vasculature of the affected limb. The chief cause of failure was arteriosclerotic change in the blood vessels. The selection of patients with embolism for operation definitely can be made on the basis of physical examination. The absence or presence of epicritic sensation is the most important physical finding. The use of sympathetic block procedures and vasodilator drugs was of little help. In fact, this practice leads to confusion and delays necessary operation.

Where properly indicated, timely embolectomy is a limb-salvaging and life-saving procedure in which success is to be expected and failure explained.

101 E. 93rd St. (28) (Dr. Blum).

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ARTERIAL EMBOLECTOMY

Seebert J. Goldowsky, M.D.
and
J. Robert Bowen, M.D., Providence, R. I.

The late results of arterial embolectomy have been assessed after 46 operations performed on 42 patients over a period of 11 years. The ages of the patients ranged from 38 to 82 years. There were 17 hospital deaths. Among the survivors there was 100% salvage of the imperiled extremities. Since every patient in this series was followed up successfully, complete attrition data were obtained, the survival rate declining progressively to 40% for 5 years and 27% for 11 years. When the operation was delayed eight hours or more after the onset of symptoms the mortality was but little higher than that after immediate operation. The data did not answer the question of whether anticoagulant therapy was preferable to surgery in this situation.

Since the first successful performance of embolectomy by the Frenchman Labey[1] in 1911, this procedure has gained, with but few dissenting voices, general acceptance as the treatment of choice in the management of peripheral arterial embolism. Among the dissenters is Wessler,[2] an advocate of early anticoagulation therapy with heparin sodium. He has concluded that embolectomy cannot be recommended as the treatment of choice in acute occlusive disease because of the high mortality associated with this procedure. A generation ago (in 1923) Key[3] reported 6 successful embolectomies in 10 attempts. This remarkable experience compares favorably with recently reported series. The most important contributions of the past 20 years have been concerned with the application of more modern and handier equipment and the availability of effective anticoagulants for local and systemic use. It is of interest that the now popular retrograde flushing procedure was described as long ago as 1930 by Lerman and associates.[4]

Purpose of Study

Larger series[5] than the one here reported can be found in the literature, some with better results, perhaps. However, after adequate search, we have failed to find a single follow-up study in any one significant series. We were curious to know the ultimate fate of patients subjected to embolectomy. Lack of any pertinent useful information led to this review of our experience. Since we have been successful in attaining a 100% follow-up, we felt it would be of value to make this material a matter of record. Furthermore, it seems worthwhile to appraise an experience with this operation in a non-university center.

Embolectomy

The study here reported is based on 46 operations performed on 42 patients over a period of 11 years, up to Jan. 1, 1959. All but one of the procedures were carried out at Rhode Island Hospital. Thirteen of these embolectomies on 12 patients were performed by one of us (S. J. G.). A small additional number of operations described as embolectomy was excluded from the study because of the difficulty of differentiating between arteriosclerotic thrombosis and true embolism on clinical or pathological grounds. In general, these latter patients, having extensive thrombosis of several days' duration, could not be classified as having acute embolic occlusion.

Population.—The patients studied included 24 women and 18 men. Their ages at the time of the first intervention ranged from 38 to 82 years, with an average age of 62.3 years. Table 1, which gives these patients' ages by decades, shows that more than one-half of the cases of acute embolic occlusion occurred in patients within the two decades from 60 to 79 years of age. The average age of 14 patients with rheumatic heart disease was 53.8 years, while that of the others was 66.5 years. In 9 of the latter 28 patients there was cardiac pathology based on coronary occlusion. Twenty-six of the total group of 42 patients had auricular fibrillation.

TABLE 1.—*Age by Decades of Forty-two Patients at First Embolectomy*

Age	No. of Patients
30-39	2
40-49	7
50-59	8
60-69	10
70-79	12
80-89	3

Limb Salvage.—Seventeen hospital deaths resulted from 46 operations, i. e., an operative mortality of 37%. There was no loss of limb among the

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From the Surgical Service and Peripheral Vascular Clinic of Rhode Island Hospital and the Surgical Service, Miriam Hospital.

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survivors. This would give a limb survival equal to the patient survival, or 63%. Among those who died, three patients had had actual amputations and four inevitable gangrene. This would provide a potential limb salvage (in 47 opportunities comprising 46 operations, and one bilateral procedure) of 85.1%.

If the above results are broken down for the periods from 1948 to 1953 inclusive and 1954 and 1958 inclusive, 18 operations were done in the first and 28 in the second period. The mortality in the first period was 33.3% (6 patients), while in the second it was 39.2% (11 patients). Evaluation of limb salvage within the same periods and with use of the figure of 47 opportunities, as indicated above, shows 2 actual or inevitable amputations out of 19 opportunities in the first and 5 out of 28 in the second group. This would yield an actual or potential limb salvage of 89.5% for the first and 82.1% for the second period. If we had elected to count each of the five aortic cases as two opportunities instead of one, the calculated potential limb salvage would have been slightly better. These small numbers do not yield statistically significant differences, but it is fair to say that there has been no obvious improvement in mortality or limb salvage. This may be accounted for in part by a more aggressive approach in late or very severe cases during the second period.

TABLE 2.—*Effect of Delay on Operative Mortality in Forty-six Embolectomies*

Time from Symptoms to Surgery, Hr.	No. of Operations	No. of Deaths	Mortality
0- 4	13	4	
4½- 8	15	6	
8½-12	10	2	
12½-18	4	3	
18½-24	2	1	
>24	2	1	
0- 8	28	12	35.7%
> 8	18	18	38.9%

Signs, Symptoms, and Pathology.—In the 46 operations reported here, 49 emboli were found in our 42 patients, of whom 2 had multiple emboli (two in each instance) and one a bilateral embolus. The majority of emboli were located in the femoral system (17 in the common femoral and 12 in the superficial femoral arteries and Hunter's canal), 5 in the aorta, 6 in the popliteal, and 4 in the axillary and brachial arteries. Since only two of the five operations on aortic emboli were successful, the mortality for this small group was 60%. A total of 13 retrograde flushing procedures were performed, the first in 1955.

TABLE 3.—*Survival After Embolectomy*

	Yr. of First Operation											Total No. of Patients
	1948	1949	1950	1951	1952	1953	1954	1955	1956	1957	1958	
No. of 1st operations	1	2	2	3	2	5	2	1	4	9	11	42
Length of survival yr.	10-11	9-10	8-9	7-8	6-7	5-6	4-5	3-4	2-3	1-2	>1	
Living at time of writing		1	1	1		1			2	5	5	16
Dead at time of writing					1	1		2	2		20	26

Table 2 analyzes the effect of the time interval from onset of symptoms to surgery. Twenty-eight of the 46 operations were performed within eight hours of onset of symptoms, while in 18 cases the time exceeded eight hours, ranging up to five days. It will be seen that the operative mortality in the first group was 35.7%, while in the second it was increased slightly to 38.9%.

In 35 of our 42 patients the heart was presumed to be the source of the emboli. However, this was verified in only five instances, four at postmortem examination and one at the time of a subsequent mitral valvuloplasty. In one case of mitral valvuloplasty no thrombus was found. In seven cases no source or origin for the emboli could be postulated on the basis of clinical evidence, and in five of these none could be demonstrated even at postmortem examinations, which included careful inspection of the aorta.

Follow-up Studies

Survival Rate.—The number of cases out of the total of 42 available for follow-up at varying periods are shown in table 3. Of the 22 patients who had had their first operation more than two years ago, 12 (54.5%) survived two years or more. Of the 18 patients operated on more than three years ago, 8 (44.4%) survived three years or longer. Of the 15 patients operated on more than five years ago, 6 (40.0%) survived five years or longer. Sixteen (38.1%) of the total of 42 patients were still alive at the shut-off date. However, 5 of these 16 were operated on during the last year. In other words, of the 31 patients first operated on more than one year ago, only 11 (35.5%) were still alive at the close of this study, and of the 22 patients operated on more than two years ago, only 6 (27.3%) were alive as of the same date. Thus it appears that, although the chances of surviving an initial embolectomy exceed 60% (26 out of 42, or 61.9%), the survival rate declines progressively to 40% for five years, with a continuing, progressive decline thereafter.

Long-term Anticoagulant Therapy.—Our experience with long-term anticoagulant therapy has been appreciable and fairly satisfactory. Twelve of our 42 patients eventually were placed on long-term therapy, usually with bishydroxycoumarin (Dicoumarol). These patients have been undergoing treatment for periods ranging from seven and one-half months to seven and one-half years (table 4). Nine of these 12 patients, including one treated for seven and one-half years, are still living; each of two minor and one major embolic episodes which occurred among them was due to temporary lack of control. The three deaths among the 12 patients receiving anticoagulant therapy were due, respectively, to coronary occlusion, retroperitoneal hemorrhage after sympathectomy, and inanition 16 months after an extensive resection of the small intestine for embolic infarction. Thus, none of the deaths in this group was attributable directly to a major embolus, and only one patient required a subsequent embolectomy. Neither of two patients on whom a mitral valvuloplasty had been performed has had further embolic episodes.

Sequelae.—Of the 42 patients in our series, 2 had two and one patient three separate embolectomies. So far as can be determined from their histories, 16 patients had had previous nonsurgical embolic episodes of all types, 11 having had two episodes. Subsequent related surgical procedures were as follows: lumbar sympathectomy, four; thigh amputation, three; mitral valvuloplasty, two; repair of evisceration after aortic or iliac exploration, two; and one each of extensive jejunal resection for mesenteric embolism, exploration without resection for extensive inoperable mesenteric embolism, and fasciotomy for muscle edema and ischemia. Two patients had drop foot from ischemic neuritis. Muscle function eventually returned in one of these; no information is available on this point for the other. Restoration of peripheral pulses was not uniformly accomplished. Satisfactory, late clinical results as regards adequate peripheral circulation were generally obtained, however, despite failure of peripheral pulses to return. Late ischemic sequelae presented a serious problem in only one case in this series.

TABLE 4.—*Effect of Long-term Anticoagulation Therapy in Twelve Patients*

Length of Treatment, Mo.	Living	Dead
6-12	3	0
12-24	3	2
24-36	2	0
Over 36	1 (7½ yr.)	1
Total	9	3

The causes of death in the 17 postoperative fatalities and in the 9 late deaths are listed in tables 5 and 6.

Summary and Conclusions

Our follow-up study on 42 patients who had been subjected to 46 peripheral arterial embolectomies resulted in the following findings: 1. The over-all operative mortality for peripheral arterial embolectomy was 37%. 2. The chances of surviving the first embolectomy were 61.9%. 3. The chances of surviving the first embolectomy and living three years or longer were 44.4%. 4. The chances of surviving the first embolectomy and living five years or longer were 40%. 5. The attrition continued significantly after the five-year period. Of all patients operated on more than two years ago, but within the 11 years of this study, only 27.3% still survive. 6. Initial high mortality is a serious problem. Limb salvage, on the other hand, is satisfactory. The nature of the disease in these very ill patients is the most important factor contributing to this mortality and to the continued attrition thereafter. 7. Late peripheral circulatory sequelae have not, for the most part, been a serious problem. 8. Long-term anticoagulation therapy has been found to be a valuable prophylactic procedure against further emboli. It is indicated in auricular fibrillation as well as in occasional cases of persistent mural thrombus with recurrent embolus after myocardial infarction. Atrial appendectomy, although resorted to only twice in this series, undoubtedly has a place in properly selected cases of rheumatic valvular disease. 9. Delay in instituting surgery was less of a factor in mortality than we

TABLE 5.—*Causes of Seventeen Deaths After Embolectomy*

Postmortem Diagnosis
  Retroperitoneal hematoma after contralateral sympathectomy (bishydroxycoumarin [Dicumarol])
  Congestive failure; rheumatic heart disease; pneumonia
  Bronchopneumonia; renal failure
  Superior mesenteric embolus; intestinal infarction; peritonitis
  Superior mesenteric embolus; intestinal infarction
  Massive pulmonary embolus; myocardial infarction; superior mesenteric embolus; thrombosis iliac vein into vena cava
  Bleeding duodenal ulcer; multiple emboli: kidneys, superior mesenteric, spleen
  Cerebral embolus
Clinical Diagnosis
  Arteriosclerotic heart disease; impending gangrene, other leg
  Congestive failure
  Mesenteric embolus, confirmed by abdominal tap
  Carcinoma of lung with cachexia
  Hepatorenal failure
  Cerebrovascular accident (embolic)?
  Electrolyte and fluid loss from gastrointestinal fistula after previous gastrectomy; myocardial infarction
  Old cerebrovascular accident; vascular collapse
  Myocardial infarction; pulmonary edema

TABLE 6.—*Causes of Late Deaths After Embolectomy*

Postmortem Diagnosis
  Inanition late after extensive intestinal resection for embolic infarction
  Carcinoma of esophagus
  Hypertensive cardiovascular disease; nephrosclerosis; renal failure
Clinical Diagnosis
  Cerebral embolus
  Cerebral embolus
  Mesenteric embolus, inoperable, confirmed by surgery
  Arteriosclerotic heart disease; bronchopneumonia
  Coronary occlusion
  Coronary occlusion

had anticipated. Inevitably it must, however, affect both limb salvage and mortality to some extent. 10. This study neither clearly supports nor unequivocally refutes Wessler's contention that anticoagulation therapy with heparin rather than surgery is the treatment of choice in acute arterial embolism. Our experience would indicate, however, that his conclusions may have validity in patients who are poor surgical risks.

209 Angell St. (6) (Dr. Goldowsky).

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ACUTE ATTACKS OF GOUT PRECIPITATED BY CHLOROTHIAZIDE-INDUCED DIURESIS

Leon J. Warshaw, M.D., New York

Side-effects due to chlorothiazide, an orally administered diuretic, have been infrequent, and the difficulties incurred have not been serious. Increased potassium excretion causes hypopotassemia in patients who have taken the drug continuously for long periods of time, but this can usually be countered by adding supplementary potassium compounds to the patient's diet. Chlorothiazide has also produced hyperuricemia and, in patients with a gouty diathesis, has precipitated acute attacks of gouty arthritis. Two such cases are reported. The presence of gouty arthritis should be suspected in patients treated with chlorothiazide or one of the other benzothiadiazine compounds and who complain of aching joints and, especially, of painful feet. Stopping the administration of the drug usually suffices to control the arthritis, but, when arthritis is severe, use of colchicine may be necessary.

Chlorothiazide has recently become popular as an orally administered diuretic and has been used in the treatment of essential hypertension to enhance the effects of specific hypotensive agents. Although earlier claims of its diuretic potency on oral administration being superior to that of intramuscularly injected meralluride sodium have not been substantiated,[1] it has proved to be a reasonably effective oral diuretic both in the treatment of congestive heart failure and in maintenance of cardiac compensation once it has been restored.[2] The freedom of its use, with doses being given daily and twice daily, without interruption over long periods of time, has probably been more responsible than its allegedly superior potency for many of its triumphs as a diuretic.

Untoward effects after its use have, at least thus far, appeared relatively infrequently. Except for the tendency toward hypopotassemia, which can be controlled by the prophylactic administration of supplementary potassium compounds, these have not appeared to be consequential.[2] Recently, however, cases of gout apparently precipitated by chlorothiazide-induced diuresis have been observed. Because of the implications of this type of reaction, with regard to the long-continued use of chlorothiazide and the othe [illegible] derivatives that have since been introduced, it appeared desirable to report two of these cases in detail.

Report of Cases

Case 1.—A 40-year-old man had been under treatment for a postphlebitic syndrome of the right [illegible] the residue of two classic attacks of acute

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From the Cardiovascular Research Unit, Beth Israel Hospital.

thrombophlebitis. The first had occurred three years earlier as a complication of acute erysipeloid cellulitis of the upper part of the thigh. The second attack followed in a little less than a year and was associated with cellulitis of the foot complicating an acute flare-up of long-standing dermatophytosis. Except for the generalized aching that accompanied the acute febrile illness, he denied any symptoms suggestive of arthralgia or arthritis. Urologic investigation of an episode of painless gross hematuria during his first attack of phlebitis (attributed to anticoagulant therapy, despite blood prothrombin times well within the usual therapeutic range) revealed no evidence of renal disease. The serum uric acid level was normal at that time.

The rest of the history was essentially noncontributory except that it indicated a persistent tendency toward overweight. About once every two years, the patient would partake of a high-protein, low-calorie diet featuring at least two servings of beefsteak daily. On this regimen he would lose weight at an average rate of about 2 to 4 lb. (0.9 to 1.8 kg.) per week and would usually maintain it until a total of about 30 lb. (13.6 kg.) had been lost. On a number of occasions he had also used a proprietary reducing medicament or a dextro amphetamine sulfate preparation prescribed for him by his personal physician. The only difficulty ever associated with these weight-reduction stints was the tendency for the lost pounds gradually to reaccumulate.

After the episodes of phlebitis, this reaccumulation of weight appeared to intensify his postphlebitic syndrome, the symptoms of which were edema of the leg, frequent twinges of pain along the veins reminiscent of the pain experienced during the acute phlebitis, and fatigue, both generalized and of the involved extremity.

Sodium restriction and injections of mercurial diuretics had seemed to reduce somewhat the swelling and discomfort in the leg at the time of the acute phlebitis. Chlorothiazide, which had since become available, was substituted for the mercurial diuretic therapy; the dose was 1.0 Gm. twice a day by mouth. The first few doses appeared to produce satisfactory diuresis, a loss of 4 lb. (1.8 kg.) being recorded after 24 hours (fig. 1).

On the third day therapy was interrupted by the acute onset of fever, malaise, pain, tenderness, and signs of acute inflammation involving the entire dorsum of the right foot and the ankle. Although far from similar in appearance, this was attributed to a flare-up of the cellulitis of that foot from which the patient had apparently recovered several months earlier. A broad-spectrum antibiotic was prescribed and he was instructed to "force" fluids. When 0.6 Gm. of aspirin every three or four hours failed to relieve his discomfort, codeine was prescribed. The symptoms and signs diminished at a satisfactory rate; he was afebrile in 48 hours and seemed completely recovered after five days.

Several months later, having abandoned this reducing attempt because of the acute symptoms, he resumed the diet, salt restriction, and the doses of chlorothiazide described above. Once again, diuresis resulted. It was followed two days later by a return of the fever, malaise, and a similar inflammatory involvement. This time, however, the latter involved both ankles and the region of the right first metatarsophalangeal joint and appeared much less like cellulitis than like an acute attack of gout. The serum uric acid level was 6.2 mg.%. A course of colchicine therapy (0.5 mg. every hour for eight doses) produced prompt improvement. Within 24 hours, he was afebrile and the inflammatory signs and symptoms had largely subsided. He was given doses of probenecid regularly, and one week later the serum uric acid level had fallen to 3.7 mg.%.

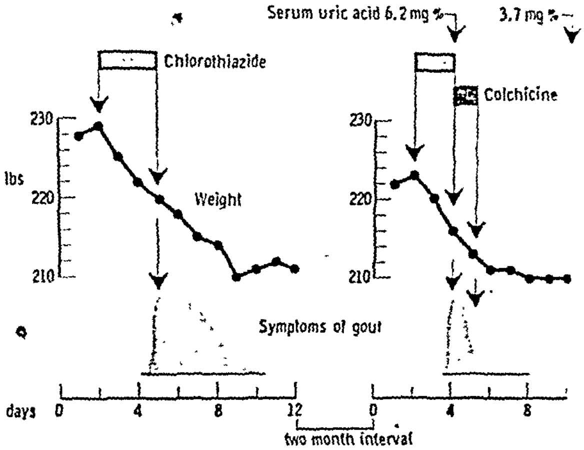

Fig. 1 (case 1).—Data obtained during two episodes of gout precipitated by chlorothiazide (dose, 2 Gm. per day) in 40-year-old man with postphlebitic syndrome and obesity.

Probenecid therapy has been maintained to the time of this writing, and there have been no further clinical indications of gout in the little over a year that has elapsed since his last attack. He has refused additional trials of diuretic therapy.

Case 2.—A 48-year-old man with rheumatic mitral and aortic valvular lesions was seen because of moderate congestive heart failure. This was his first experience with this syndrome. Except for the heart disease, the history was essentially negative. Attacks of classic migratory polyarthritis had accompanied his childhood episodes of rheumatic fever, and, since then, he had seemed to be particularly susceptible to vague arthralgias and myalgias. These were induced by respiratory infections, physical fatigue, and occasionally by abrupt changes in weather; they were not severe and usually subsided spontaneously or after he took a few doses of aspirin. On at least two occasions, more than 10 years before, these episodes had been more severe and persistent and had featured pain and swelling of the feet. During one such episode, a physician had suggested gout as a diagnosis and had prescribed a colchicine preparation, with excellent results. A special diet had also been prescribed but was abandoned by the patient soon after his recovery.

The congestive failure was treated by a previously described regimen[2] featuring digitalization, sodium restriction, and daily use of a diuretic (chlorothiazide, 1.0 Gm. by mouth). A satisfactory response was noted; the patient lost 13 lb. (5.9 kg.) of extracellular fluid in three days, and the symptoms of his failure were relieved. However, on the third day of diuretic therapy, there was an abrupt onset of fever and typical acute gouty arthritis of the left first metatarsophalangeal joint. The serum uric acid level eight hours after the onset of this syndrome was 5.4 mg.%. Diuretic therapy was interrupted and a course of colchicine was given, with a prompt subsidence of the gout. Probenecid was given (1.0 Gm., then 2.0 daily), and after a week, the serum uric acid level fell to 3.0 mg.%. While the therapy with probenecid was still being continued, intramuscular injections of meralluride sodium, first 1.0 and then 2.0 cc., were given daily. The resultant diuresis, although not as marked as that observed initially, produced an additional loss of 8 lb. (3.6 kg.) and was otherwise without incident (fig. 2).

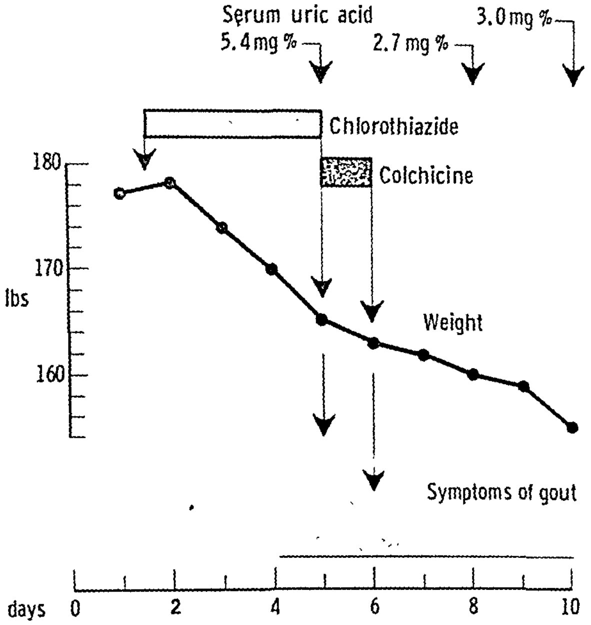

Fig. 2 (case 2).—Data obtained during period of acute gout precipitated by chlorothiazide (dose, 1 Gm. per day) in 48-year-old man with rheumatic heart disease and in moderate congestive failure.

Comment

The occurrence of hyperuricemia in patients receiving chlorothiazide has been reported previously. One case was found in a group of 87 patients with fluid retention treated with chlorothiazide in a clinical study of its effectiveness as a diuretic agent.[2] Since serum uric acid levels had been determined in only a few of the cases at that time, it is probable that there may have been more. Other instances of hyperuricemia were subsequently found among those patients and in others given similar treatment since that time. In their study of the effects of chlorothiazide on electrolyte balance, Laragh and associates[3] found a significant elevation of the serum uric acid level in six of their eight patients, which returned promptly to normal on cessation of chlorothiazide therapy. This occurred without elevation of the urea nitrogen concentration. Although preliminary serum uric acid determinations had not been made, Monroe and colleagues[4] found this value to be significantly elevated in seven of nine patients who had been *receiving chlorothiazide continuously for periods* up to 10 months in duration. The serum uric acid levels tended to fall when the drug was not used for 7 to 10 days and to rise again when its administration was resumed.

Hyperuricemia and gout.—In all of these cases of hyperuricemia associated with chlorothiazide administration, no symptoms were noted and none of the patients were thought to have gout. Recently, however, Oren and associates,[5] who found elevated uric acid levels ranging from 6.3 to 10.0 mg.% in each of a group of 12 patients who had used chlorothiazide for long periods of time, noted that 2 patients complained of joint pains, especially in the feet. In one patient these symptoms appeared about three months after the institution of chlorothiazide therapy, disappeared a few days after it was interrupted, returned two weeks after it was resumed, and disappeared again when use of chlorothiazide was finally abandoned. Their second patient developed painful feet about six months after beginning chlorothiazide therapy, and three months later he was found to have typical physical signs and roentgenographic evidence of gouty arthritis of the right great toe. This patient was subsequently discovered to have had the clinical signs and roentgenographic evidence of gout several years prior to the chlorothiazide therapy. On this occasion, cessation of chlorothiazide therapy was followed by subsidence of all of the signs and symptoms.

Gutman[6] noted the occasional appearance of hyperuricemia due to chlorothiazide therapy and also precipitation of acute gouty arthritis in patients with a history of gout or in whom gout was presumably latent. He remarked that both the hyperuricemia and the acute attacks of gout in gouty subjects occur more regularly after hydrochlorothiazide administration and considered them a serious drawback to the use of this drug.

The mechanism by which chlorothiazide produces hyperuricemia is not known. The studies of Demartini[7] indicated that the prolonged use of this compound interferes with the renal excretion of urates. He believed, as did others who have studied this phenomenon, that explanations on the basis of a presumed increase in the catabolism of nucleic acids are probably not correct. Whether the mechanism is the same as that producing the hyperuricemia of naturally occurring gout is not yet known. Nor has it been established whether this is a purely incidental occurrence or one that is found only in patients with latent gout. The well-known absence of correlation between serum uric acid levels and clinical symptoms in patients with known gout makes it unlikely that a satisfactory answer will be found in the observation of acute articular episodes. The recent report by Kohn and Prozan,[8] suggesting a relationship between hyperuricemia and coronary atherosclerosis with myocardial infarction, makes it urgent that the true significance of the hyperuricemia be established.

Precipitation of Articular Episodes.—The mechanism by which an acute articular episode is precipitated in a gouty patient is also not understood. Some of the various agents held to have caused this phenomenon are acute infections, acute blood loss, prolonged bed rest, surgical operations, emotional trauma, and local x-ray therapy. Various drugs, including penicillin, thiamine chloride, vitamin B_{12}, insulin, liver extract, and ergotamine tartrate, have also been presumed to cause an acute attack.

Probably the first to note the association of acute gout with a diuretic agent was Hench,[9] who merely made a passing allusion to mersalyl sodium (Salyrgan) theophylline as one of the agents capable of activating quiescent gout in a gout-susceptible patient.

Several years later, Price[10] reported five patients with histories of gout in whom an acute attack was immediately preceded by "critical diuresis" produced by a diuretic regimen consisting of injections of mersalyl on alternate days. Although the previous doses had apparently produced adequate diuresis, the attack of gout appeared to be related to the greatest urinary output produced by successive doses of the diuretic. Price called this the "critical diuresis" and compared it to the much less marked spontaneous diuresis frequently observed to precede the acute exacerbations in gouty persons who do not have heart disease. Because all five of his patients died of heart disease within a few weeks to a few months after their attacks of gout, Price considered the mersalyl-induced attack to signify a bad prognosis. This prognostic implication has been challenged by Talbott,[11] who has also observed acute gout after induced diuresis. The latter's view appears to be supported by the cases described by Oren and associates[5] and those reported above.

With the possible exception of patients with pernicious anemia who were generally maintained on high-purine diets, in whom acute articular episodes might be precipitated by injections of liver extract, there has been no relationship between the biochemical phenomena associated with gout and those that attend the administration of the drugs observed to precipitate acute attacks. In all instances, the mechanism of this reaction was thought to be general rather than specific. In the cases that followed administration of a diuretic agent, the mechanism was thought to be the abrupt shift in electrolytes produced by the diuresis rather than any specific effect of the diuretic agent itself on urate metabolism. In patients with acute gout induced by chlorothiazide diuresis, this concept is clouded by the frequent observation of hyperuricemia after chlorothiazide therapy. However, the appearance of clinical symptoms does not appear to be related to the degree of serum uric acid level elevation. Clarification will have to await a better understanding of the pathophysiology of gout, the relationship between the metabolism and excretion of uric acid and the acute articular episode, and, finally, whether the hyperuricemia produced by chlorothiazide involves a similar mechanism or merely represents a nonspecific effect of this drug on the kidneys.

Prevention of Articular Episodes.—For the present, it appears propitious to avoid the use of chlorothiazide and other benzothiadiazine compounds in patients with a history of gout and to suspect the possibility of gout in patients treated with these drugs who complain of aching and painful joints, especially of the feet. Since these complaints are commonly encountered among patients in the age groups likely to require chlorothiazide therapy, such a suspicion will be aroused rather frequently. Although it would be interesting to observe the fluctuations in serial serum uric acid level determinations in these persons, the lack of correlation between this finding and clinical gout would render it of little value in establishing the diagnosis. A prompt subsidence of the symptoms after the cessation of chlorothiazide therapy and, when severe enough, the concurrent administration of a standard course of colchicine, would tend to confirm it. In such cases, it would probably be wise to abandon therapy with chlorothiazide in favor of one of the other diuretic agents which induce hyperuricemia and acute gout much more rarely, if at all.

The possible use of probenecid to prevent the retention of uric acid and thereby diminish the likelihood of such acute articular episodes has been suggested. Its value in the management of gout is well established. Beyer[12] demonstrated in dogs that the simultaneous intravenous administration of probenecid and chlorothiazide diminished the renal clearance of the latter but did not appear to alter greatly its diuretic action. This is countered by personal experiences (case 2) in which probenecid administration appears to have been followed by a response to a subsequent diuretic agent less marked than was anticipated. It remains to be determined whether such inhibition of diuresis is sufficient to make the combination of probenecid and chlorothiazide significantly less satisfactory than the use of another diuretic agent alone. Even if this were so, additional studies would be needed to determine whether the simultaneous administration of probenecid would significantly compromise the usefulness of chlorothiazide in antihypertensive regimens.

Summary and Conclusions

Acute articular episodes of gout were precipitated by chlorothiazide-induced diuresis in two patients. Hyperuricemia is a relatively frequent concomitant of chlorothiazide administration and appears to result from diminished urate excretion. Gout should be suspected in patients who, under treatment with chlorothiazide or with one of the other benzothiadiazine compounds, complain of arthralgia. The symptoms and the hyperuricemia subside promptly when chlorothiazide therapy is interrupted. Colchicine may be used when the arthritic symptoms are severe.

Although the mechanisms by which chlorothiazide produces hyperuricemia, and the relationship between this hyperuricemia and the clinical manifestations of gout, are not clearly understood, these phenomena are a drawback to the use of this drug, especially in patients with a history of gout.

1501 Broadway (36).

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ANTIBIOTICS IN DENTAL CONDITIONS.—Antibiotic therapy has been abused by both the dental and medical professions. Antibiotics are not innocuous agents and their use is often attended by complications far in excess of the disease entity they were supposed to cure. When these agents are used, they must be used long enough and in dosage strong enough to give a therapeutic result. Antibiotics are not a substitute for careful diagnosis or surgery or meticulous operative technic. If good antibiotic medicine is to be practiced, constant study of the current dental and medical literature on the part of the dentist or physician is essential, and changes of trends in therapy must be noted. Full use should be made of relevant data. The regular use of antibiotics is fully justified when dental surgery is to be performed in patients who are afflicted with any of the following conditions: rheumatic heart disease, congenital heart disease, subacute bacterial endocarditis, rheumatoid arthritis, diabetes or renal disease, or for patients on steroid therapy or receiving radiation for malignant tumors of the head and neck. It must be remembered that these patients are all debilitated to some extent, at least physiologically if not physically, and should not be subjected to any secondary dental infection if at all possible. Usually broad spectrum antibiotics have been found to be most adequate.—E. J. Degnan, D.D.S., Use and Abuse of Antibiotics in Dentistry, *Journal of Oral Surgery, Anesthesia and Hospital Dental Service,* November, 1959.

LABORATORY DATA ON THE DETROIT POLIOMYELITIS EPIDEMIC—1958

Gordon C. Brown, Sc.D., Ann Arbor, Mich., Willard R. Lenz, M.D., Detroit
and
George H. Agate, M.D., Lansing, Mich.

During an epidemic of poliomyelitis in Michigan in 1958, virological and serologic studies were carried out with specimens from 1,060 patients. Fecal specimens from 869 patients yielded no virus in 401 cases, poliovirus in 292, ECHO (enteric cytopathogenic human orphan) virus in 100, Coxsackie virus in 73, and unidentified virus in 3 cases. Serums from 191 patients from whom no fecal specimens were obtainable showed no antibody changes in 123 cases but did show changes diagnostic for poliovirus in 48, ECHO viruses in 14, and Coxsackie virus in 6. In a large number of paralytic as well as nonparalytic patients poliovirus was not the cause. Frequency studies showed that there were no obvious clinical differences among infections with Coxsackie, ECHO, and poliomyelitis viruses. Coxsackie and ECHO viruses were responsible for more cases of "nonparalytic poliomyelitis" and "aseptic meningitis" than was poliovirus itself. This, added to the fact that two immunological types of the poliovirus were involved in the epidemic, suggests the difficulty to be anticipated in future programs of immunization.

During 1958 the state of Michigan experienced its largest epidemic of poliomyelitis in many years, with more than 1,200 cases reported to the state department of health. Most of the victims resided in Detroit and its immediate environs, and a preliminary report describing the occurrence and distribution of cases in that metropolitan area has been published.[1]

For several years the virus laboratory of the University of Michigan has performed diagnostic tests on specimens obtained from patients diagnosed as having poliomyelitis and has reported the findings to the hospitals that submitted the specimens, to the state department of health, and to the United States Public Health Service. Hence, prompt arrangements were made for the collection of stool and blood specimens as well as clinical histories on the cases occurring in 1958 as soon as the patients were hospitalized. Virological laboratory tests were carried out on 1,060 persons, probably the greatest percentage of victims of a large epidemic of poliomyelitis ever to be subjected to laboratory investigation.

Method of Testing

Through the cooperation of the medical staffs of the various hospitals involved, stool specimens and serums obtained during the acute and convalescent phases of poliomyelitis were collected and sent to our laboratory. Appropriate information such as name, age, sex, address, date of onset, vaccination history, and clinical findings accompanied the specimen obtained from each patient. Stool specimens were prepared by the addition of three volumes of tissue-culture fluid containing antibiotics, the mixture then being shaken in Lusteroid tubes with glass beads for 20 minutes. The resulting emulsions were centrifuged first at 2,000 rpm for 30 minutes and then at 10,000 rpm for 45 minutes, after which the supernatants were placed directly into tubes containing monolayer cultures of monkey-kidney cells. Specimens from paralytic patients were retested if the findings had been negative for virus on the first attempt. Virus isolations, as determined by cytopathogenicity, were typed with known hyperimmune reference serums, to determine their immunological identity. If an agent was found not to be poliovirus, it was tested against all 24 types of enteric cytopathogenic human orphan (ECHO) virus serums and against those of Coxsackie virus types A9 and B1 through B5.

Paired serums obtained during the acute and convalescent stages of the illness were tested for antibody content by neutralization tests in plastic panel cultures of monkey-kidney cells against 100 tissue-culture doses (TCD_{50}) of appropriate reference viruses.

Results

Stool specimens were available from 869 patients, and on 191 additional persons from whom no stool specimens had been collected a diagnosis was made by testing the serums obtained during the acute and convalescent phases of poliomyelitis. The results of attempted virus isolation from stools are presented in table 1, where it will be seen that an agent was obtained from 245 of 567 patients whose diagnosis on admission had been nonparalytic, or suspect poliomyelitis or aseptic meningitis. Virus was isolated from 223 of 302 patients who had been

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From the Department of Epidemiology and Virus Laboratory, School of Public Health, University of Michigan (Dr. Brown); Communicable Disease Division, Herman Kiefer Hospital, Department of Health (Dr. Lenz); and Acute Communicable Disease Section, Michigan Department of Health (Dr. Agate).

classified as having paralytic or bulbar cases of poliomyelitis. Table 2 presents the results of serologic tests on patients from whom no stool specimens were available, and it will be seen that the etiology of illness could be identified both in an additional 35 of 143 nonparalytic patients as well as in 33 of 48 paralytic patients. Because of these extensive tests several significant observations can be made.

TABLE 1.—*Distribution of Virus Isolated from Stools of 869 Poliomyelitis Patients*

		Virus in 567 Nonparalytic Cases, No.						Virus in 302 Paralytic, Bulbar Cases, No.			
No. of Vaccinations	Total	Negative	Polio	ECHO	Coxsackie	Undetermined	Total	Negative	Polio	ECHO	Coxsackie
None	199	109	44	30	16		210	43	164	2	1
1	34	19	6	4	5		31	5	26		
2	90	53	9	15	11	2	27	10	17		
3	244	141	15	48	39	1	34	21	11	1	1
Total	567	322	74	97	71	3	302	79	218	3	2

Types of Poliomyelitis Virus.—The epidemic involved two immunological types of poliomyelitis virus. Of the poliomyelitis viruses recovered from nonparalytic patients, 57 were found to be type 1 and 17 type 3. Of the polioviruses obtained from the paralytic patients, 177 were shown to be type 1 and 41 type 3. Serologic tests on specimens obtained from patients from whom no fecal specimen was available likewise indicated the presence of these two types of virus as causative agents. Two paralytic patients appeared to have dual poliovirus infections, since both types of virus were isolated from the same stool specimen. Two children, both in the same family, were hospitalized on Aug. 8, 1958, with a diagnosis of nonparalytic poliomyelitis shown to be due to a type 1 virus infection. After recovery and release they were both readmitted to the hospital on Oct. 1, 1958, with the same diagnosis, and this time type 3 virus was recovered. Serologic tests on blood specimens obtained during both illnesses proved that these children had each experienced separate infections with two different immunological types of poliomyelitis virus within a period of two months.

TABLE 2.—*Results of Serologic Tests (Serums from Acute and Convalescent Phases) Performed on 191 Poliomyelitis Patients (Stool Specimens unobtainable)*

		Virus in 143 Nonparalytic Cases, No.					Virus in 48 Paralytic Cases, No.			
No. of Vaccinations	Total	Negative	Polio	ECHO	Coxsackie	Total	Negative	Polio	ECHO	Coxsackie
None	46	34	8	2	2	31	8	21	2	
1	3	3				7		7		
2	23	18	5			3	2	1		
3	71	53	5	10	3	7	5	1		1
Total	143	108	18	12	5	48	15	30	2	1

Viruses Other than Poliomyelitis.—ECHO viruses were isolated from 97 of the persons hospitalized with nonparalytic infections; in 94 of these the agents were identified as type 9 ECHO virus and in 3 as type 6. Nonparalytic infections in 71 persons were caused by Coxsackie viruses, of which 55 were due to type B5. Coxsackie type A9 was isolated 9 times, type B2 twice, and type B3 thrice; three isolates are still unidentified. Thus these viruses were the cause of nonparalytic disease more frequently than was poliovirus (see table 1).

It was of considerable interest that the ECHO 9 virus was associated with paralytic disease in three persons and the Coxsackie B5 in two. Serologic tests indicated that three additional paralytic illnesses were caused by these agents.

Relation of Vaccination to Incidence.—Table 1 clearly shows that most of the virus-confirmed cases of poliomyelitis had occurred in persons who had received no poliomyelitis vaccine. Forty-four of the 74 nonparalytic patients and 164 of the 218 classified as paralytic were unvaccinated. The number of virus-confirmed paralytic cases decreased among persons who had received one or more doses of vaccine, as is borne out by the fact that only 11 patients were found to have been vaccinated three or more times. Table 3 combines the results in tables 1 and 2 and expresses the findings in terms of the percentage distribution of all patients according to their vaccination history.

The percentage distribution of patients with virus-confirmed poliomyelitis who had a history of three doses of poliovirus vaccine was definitely lower than that among persons with fewer inoculations. While there was little difference between the unvaccinated and those reported to have had only one dose, the percentage of negative findings increased progressively in persons who had been given two and three doses of poliovirus vaccine. The percentage of nonparalytic cases confirmed as poliomyelitis decreased steadily from 21% among the unvaccinated to 6% in patients who had received three injections. Among the nonparalytic cases it can be seen that, regardless of the number of persons in each vaccine group, from 58 to 63% were negative for virus, a remarkably constant finding. The occurrence of ECHO and Coxsackie virus infections was not influenced by poliomyelitis vaccination.

Correlation of Serology and Virology.—Antibody determinations were possible on 185 of the 292 patients from whom poliovirus had been isolated. In all but two of these patients the antibody pattern was consistent with the immunological type of virus recovered. Most of the serums obtained in the acute phase of the disease contained type-specific antibodies to a titer of 1/64 to 1/256, confirming previous observations that antibody develops early during the incubation period in this disease. Only 52% of patients showed a further rise in titer during convalescence, but the presence of specific antibodies to one type in high titer in the absence of antibodies to the other types is known to have significance in the diagnosis of poliomyelitis. In fact, the present results closely approximate those reported in the final report of the field trial in 1954.[2]

TABLE 3.—*Percentage Distribution of 1,060 Patients with Poliomyelitis by Vaccination History*

		Nonparalytic Cases, Virus, %						Paralytic Cases, Virus, %			
No. of Vaccinations	Total	Negative	Polio	ECHO	Coxsackie	Undetermined	Total	Negative	Polio	ECHO	Coxsackie
None	245	58	21	13	7		241	21	77	2	
1	37	59	16	11	13		38	13	87		
2	113	63	12	13	10	2	30	40	60		
3	315	62	6	18	13	0.3	41	63	29	2	4
	710						350				

Paired serums were available for testing on 201 of the 322 nonparalytic patients from whom no virus could be isolated. With use of the same criteria of antibody patterns as those applied in the patients from whom virus was isolated, only 23, or 11%, of the nonparalytic patients showed antibody changes diagnostic of poliomyelitis and one for ECHO type 9 infection. Paired serums were obtained from 58 of the 79 virus-negative paralytic patients, and 14, or 24%, of these showed changes diagnostic of poliomyelitis. Of these 14 paralytic patients, 11 whose serologic findings were positive were unvaccinated, and the remaining 3 had received two doses of poliovirus vaccine. Thus the serologic results obtained in specimens from patients from whom no virus was isolated indicate that the isolation technique was about 90% effective for the nonparalytic patients and 75% effective with those who were paralytic, suggesting strongly that poliovirus was not the cause of illness in a large number of both paralytic and nonparalytic patients.

ECHO virus type 9 serologic determinations were performed on 71 of the 97 patients from whom that virus had been isolated. All but one had antibodies in the specimen obtained in the acute stage of the illness, mostly of a high titer, and 49 patients, or 70%, showed a further rise in titer during convalescence. The titers of poliomyelitis antibodies remained unchanged in all but three of these patients. The concurrent rise in poliomyelitis antibody in these latter three patients suggests the possibility of otherwise undetected dual infection.

Coxsackie type B5 serologic investigation was performed for 32 of the 55 patients whose stools contained that virus. All but 3 had antibodies in the specimen obtained during the acute phase, and 23, or 72%, showed further development of antibodies during convalescence. The presence of type-specific antibodies and the demonstration of increased antibody production in about 70% of the patients from whom ECHO and Coxsackie viruses were isolated indicated that it was these agents that were responsible for the illnesses and not merely latent or carrier viruses. This is particularly significant with respect to paralytic disease. Paired serums were available from two paralytic patients from whom ECHO 9 virus had been recovered and from one patient, who had a fatal case, who excreted Coxsackie B5. In each instance there was a rise in type-specific antibodies.

Multiple Infections in Families.—There were 34 families in which two or more members were hospitalized during the epidemic. Twenty-eight families had two members hospitalized with a tentative diagnosis of poliomyelitis. The infection was shown to be due to ECHO 9 virus in eight families and Coxsackie B5 in three; all others were clearly due to poliovirus type 1 or 3. Three members from each of four families were hospitalized. Two of these families were shown to be infected with poliovirus and one with ECHO 9. Two persons in the fourth family were infected with type 1 poliovirus and one with Coxsackie B5. Of the two families with four cases, all patients were infected with type 1 poliovirus.

Age Distribution.—Table 4 shows the distribution by age of the patients examined in the laboratory. It is obvious that the virus-confirmed cases of poliomyelitis occurred predominantly in younger persons, whereas Coxsackie and ECHO virus infections were much more evenly distributed by age, especially among those less than 14 years of age, as were the persons from whom no virus could be isolated.

Correlation of Clinical and Laboratory Findings.—Since it is difficult to differentiate various enterovirus infections on a clinical basis alone, an attempt was made to collect appropriate clinical findings on as many patients as possible from whom either Coxsackie or ECHO viruses had been isolated. The percentage of occurrence of signs and symptoms associated with these infections is presented in table 5. No obvious clinical differences between the two infections were apparent; in fact, the findings showed a remarkable similarity. Furthermore, there was no predominant finding which separated either infection from nonparalytic poliomyelitis. It is of interest that a history of rash, commonly thought to be associated with ECHO 9 infection, was obtained in only 7% of such cases. The spinal fluid cell counts on most of these cases were available and are compared in table 6 with counts from patients with both paralytic and nonparalytic poliomyelitis as well as with those from patients from whom no agent could be recovered. While most of the virus-confirmed poliomyelitis patients had spinal fluid cell counts of less than 200 per cubic millimeter, infections with Coxsackie and ECHO virus were frequently associated with much higher counts, especially the former. Protein and sugar levels in the spinal fluid of patients with ECHO and Coxsackie infections were above normal, as in patients with poliomyelitis. Fluid from patients with ECHO infections, however, was characterized by the low number of polymorphonuclear cells and a very high lymphocyte count in the spinal fluid, frequently 100%. In contrast, fluid from patients with Coxsackie infections was associated with the reverse picture, i. e., high polymorphonuclear and low lymphocyte percentages.

Table 4.—*Age Distribution Among Poliomyelitis Patients Subjected to Laboratory Examination for Virus*

	Virus					
	Isolated in Patients, %					
	With Poliomyelitis		With Other Virus		Not Isolated in Patients, %	
Age, Yr.	Paralytic (211 Patients)	Nonparalytic (73 Patients)	Coxsackie B5 (54 Patients)	ECHO 9 (89 Patients)	Paralytic (68 Patients)	Nonparalytic (302 Patients)
0- 4	61	40	27	10	32	17
5- 9	21	35	27	29	10	27
10-14	6	14	29	27	12	15
Total	88	89	83	66	54	59
15-19	5	1	2	6	12	7
20-29	6	7	8	20	20	16
30+	1	3	6	7	14	18

Table 5.—*Percentage of Occurrence of Most Frequent Clinical Findings on Admission of Patients for Enterovirus Infections*

	Virus	
	Coxsackie (66 Cases)*	ECHO (83 Cases)†
Fever	95	95
Headache	71	80
Meningeal irritation	72	73
(Stiff neck or back, Brudzinski's or Kernig's sign)		
Vomiting	56	59
Pharyngeal injection	24	30
Nausea	22	20
Hyperactive reflexes	21	16
Chills, cold sweats	20	14
Sore throat	18	16

* Coxsackie type B, 57; type A, 9.
† ECHO type 9, 80; type 6, 3.

Table 6.—*Spinal Fluid Cell Count Among Poliomyelitis Patients Subjected to Laboratory Examination for Virus*

	Virus					
	Isolated in Patients, %				Not Isolated in Patients, %	
	No. with Poliomyelitis		No. with Other Virus			
No. of Cells/Cu.Mm.	Paralytic (146)	Nonparalytic (52)	Coxsackie B5 (41)	ECHO 9 (74)	Paralytic, No. (50)	Nonparalytic, No. (214)
0- 24	17	11	12	18	20	27
25- 49	16	30	12	12	8	10
50- 99	17	17	20	15	10	10
100-199	28	11	7	16	16	17
Total	*78*	*69*	*51*	*61*	*54*	*64*
200-299	6	4	7	11	14	8
300-399	6	11	10	5	10	10
400-599	4	10	7	7	8	8
600-799	2	4	12	5	6	5
800-999	2	2	10	3		3
1,000+	2	2	3	8	8	2

An additional correlation of clinical and laboratory information was made possible by the fact that 550 of the patients in the Detroit area were examined for muscle weakness 60 days after onset of disease. The results are presented in table 7 in terms of the degree of paralysis two months after infection, and they are arranged according to the clinical diagnosis at the time of admission to hospital and according to the results of laboratory tests carried out on specimens from these patients. It is obvious that most of the 308 patients considered to be nonparalytic on admission were also classified in that category two months later. Virus was isolated from only one-half of those among whom ECHO and Coxsackie viruses were equally responsible with poliovirus for the infections. Among the 242 patients originally diagnosed as

Table 7.—*Correlation of Laboratory Findings of Poliomyelitis with Muscle Examination Performed 60 Days from Onset of Illness*

Original Diagnosis		Laboratory Diagnosis		Results of Muscle Examination, No.			
Type	No.	Type	No.	NP*	P_1†	P_2‡	P_3§
Nonparalytic	308	Polio	66	56	3	4	3
		ECHO	53	52	1	...	...
		Coxsackie	41	40	...	1	...
		Negative	148	143	5	...	...
Paralytic	242	Polio	187	29	49	67	42
		ECHO	2	...	2	...	...
		Negative	53	20	11	15	7

* NP = nonparalytic
† P_1 = minor involvement
‡ P_2 = significant paralysis
§ P_3 = severe paralysis or death

paralytic, 187, or 77%, were confirmed by laboratory tests to have poliomyelitis. The vast majority of these (84%) were found to have residual paralysis 60 days after onset of the illness, and it is of interest that 83% of these paralytic patients were unvaccinated and only four, or 2.5%, had received three doses of vaccine. Twenty-one of the 29 patients who had changed to nonparalytic status by the time of the muscle examination 60 days after onset were also unvaccinated, and only one had received three doses; this indicates that vaccination was not associated with their improved muscle status. Of the original 53 paralytic patients not confirmed as having cases of virus infection only 33, or 62%, had residual paralysis after two months, only one-half were unvaccinated, and 22% had received three doses of poliomyelitis vaccine; this demonstrates that a history of complete vaccination was much more frequent among patients with paralytic cases which were not confirmed than among those whose illness proved to be poliomyelitis.

Comment

The availability of stool and blood specimens from such a high percentage of patients in a large epidemic of poliomyelitis provided an unusual opportunity to study the laboratory aspects of the infections and to elucidate information which would not have been apparent from clinical observation alone. One such example was the fact that two immunological types of poliovirus (1 and 3) were incriminated in the epidemic. This finding illustrates the necessity of immunization against more than one type of poliovirus. Examples of dual infection, either simultaneously or within short periods of time, emphasize the importance of this concept.

A correlation of virus-confirmed cases of poliomyelitis with the patients' history of vaccination clearly shows the suppressive effect of vaccine on clinically recognizable disease. This was apparent not only for the patients with paralytic cases but also for those classified as nonparalytic.

Serologic studies on large numbers of serum specimens obtained during the acute and convalescent phases of the illness served the dual purpose of confirming the etiology of the disease in cases in which a given virus had been isolated and also furnishing additional information on the serologic patterns which accompany these infections. This can be particularly valuable in instances in which no stool specimen is available for virus isolation.

The multiplicity of infection in 34 families was shown to be a characteristic of ECHO and Coxsackie viruses as well as of poliomyelitis. In fact, both poliomyelitis and Coxsackie viruses were isolated from members of one family at the same time.

The large number of ECHO and Coxsackie virus infections in persons with nonparalytic disease exemplified the increasing importance of these viruses in clinical medicine. In fact, these agents were responsible for more cases of "nonparalytic poliomyelitis" and "aseptic meningitis" than was poliomyelitis virus itself. Although a variety of enteroviruses was encountered, two in particular, the Coxsackie B5 and the ECHO 9, were found to be the most prevalent. In fact, 1958 was the second successive year of high incidence of the latter agent. Since these viruses can apparently cause a paralytic type of disease in an occasional person, consideration should be given to the development of preventive vaccines for certain of these agents. This is especially important for pregnant women, in view of the increasing recognition of neonatal deaths caused by Coxsackie B viruses, as recently summarized by Kibrick and Benirschke.[3] Two examples of this have recently been observed in our laboratory.[4] Coxsackie B2 virus was isolated from the heart, brain, lung, and intestinal contents of a child who died 15 days after birth. His mother had experienced only a low-grade fever at the time of delivery, and a sibling had a "sore throat" at that time. Coxsackie B3 virus was isolated from the heart of another infant who died five days after birth. The mother of this child had experienced only low-grade fever and malaise two days prior to delivery.

An attempt to correlate clinical findings with virus-confirmed ECHO and Coxsackie infections revealed that fever, headache, and meningeal irritation were the most frequent signs and that these infections were usually associated with higher spinal fluid cell counts than were cases of poliomyelitis.

A muscle examination performed 60 days after the onset of illness on 550 patients showed that 94% of those diagnosed as nonparalytic remained in that category regardless of the laboratory findings. Of the patients with virus-confirmed paralytic disease, 84% had residual paralysis two months later, 77% were unvaccinated, and only 2.5% had received three injections of vaccine. Fewer of the paralytic patients (62%) in whom poliomyelitis was not confirmed had residual paralysis. Although most of them were unvaccinated, 60% of those who became nonparalytic had received three injections of poliomyelitis vaccine.

Summary

Virological, or serologic determinations, or both, were performed on 1,060 patients who were hospitalized during the 1958 epidemic of poliomyelitis in Michigan. The results show that two immunological types of poliovirus were involved but also that certain types of ECHO and Coxsackie viruses were prevalent; in fact, they were together responsible

for more laboratory-proved cases of nonparalytic poliomyelitis and aseptic meningitis than was poliomyelitis virus itself. The vast majority of virus-confirmed cases of poliomyelitis occurred in unvaccinated persons, and 84% of these with paralysis still showed residual muscle impairment 60 days later.

109 S. Observatory St. (Dr. Brown).

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HEAD-TILT METHOD OF ORAL RESUSCITATION

James O. Elam, M.D., David G. Greene, M.D., Max A. Schneider, M.D., Buffalo
Henning M. Ruben, M.D., Copenhagen, Denmark, Archer S. Gordon, M.D., Ph.D., Los Angeles
Robert F. Hustead, M.D., Donald W. Benson, M.D., John A. Clements, M.D., Baltimore
and
Arne Ruben, M.D., Karlskrona, Sweden

Mouth-to-mouth and mouth-to-nose methods of artificial respiration are simplified and made more effective if the patient's neck is extended by the procedure here described. With the patient in the supine or semilateral position, the rescuer uses one hand to tilt the patient's head as far back as possible. He uses his other hand to pull the patient's chin upward. Circumstances determine whether the rescuer will apply his mouth to the mouth or the nose of the patient. The use of adjuncts like tubes and masks by untrained laymen in order to avoid direct contact is not recommended.

Since the publication of the symposium on mouth-to-mouth resuscitation in The Journal, May 17, 1958, page 317, improved techniques have been established for performing expired air resuscitation, now called oral resuscitation. Results from a coordinated program of investigation in seven research centers are in agreement about the advantages and workability of the simplified technique as regards effectiveness, practicality, and ease of learning and remembering.

In December, 1958, studies in apneic unconscious volunteers and patients, both curarized and noncurarized, were initiated in seven research centers by us and by cooperating rescue personnel in six metropolitan areas: Buffalo; New York City; Los Angeles; Copenhagen, Denmark; Karlskrona, Sweden; and Zurich, Switzerland. After one year of these coordinated studies in over 1,000 anesthetized human beings, results of use of the head-tilt oral method, with inflation through the victim's nose, have been uniformly satisfactory except in the group of newborn infants, which involves special problems. These extensive successful trials of the head-tilt oral resuscitation method prompt the revision of previously recommended methods, which it supersedes. This simple technique has already been taught and demonstrated to over 10,000 lay trainees.

Difficulties with Previous Techniques

Control of the air passages by (*a*) pulling on the jaw with the thumb in the victim's mouth or (*b*) pushing upward at the angles of the jaw presents problems in performance and teaching. Difficulties in performance have been as follows. 1. Leakage around the rescuer's thumb in the victim's mouth is often excessive. 2. Inflation of the relaxed victim's stomach during both mouth-to-mouth methods has been a frequent complication, aggravating passive regurgitation of stomach contents. 3. Trismus has complicated or prevented inflation through the victim's mouth. (For example, the 1959 President's

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From the Roswell Park Memorial Institute (Dr. Elam); the University of Buffalo School of Medicine (Drs. Greene and Schneider); the Finsen Institute (Dr. H. M. Ruben); the Children's Hospital (Dr. Gordon); Johns Hopkins University School of Medicine (Drs. Hustead and Benson); Army Chemical Center, Maryland (Dr. Clements); and Centrallazarettet (Dr. A. Ruben).

medal of the National Safety Council was awarded for a successful mouth-to-nose resuscitation of an asphyxiated victim in an industrial accident. The victim was found deeply cyanotic and "rigidly unconscious." His jaws were too tightly clenched to be opened. Head-tilt and mouth-to-nose inflations restored full consciousness in three minutes.) 4. Both methods are fatiguing for the rescuer's hands. 5. Insertion of the thumb in the victim's mouth through sharp teeth is hazardous, especially in near-conscious victims.

Difficulties in teaching may be summarized as follows. 1. Pulling on the jaw with the thumb or pushing upward at the angles of the jaw involves numerous fine details in technique which cannot be learned by some laymen. The average layman, unaware of the anatomy of airway obstruction, has difficulty understanding and remembering the rationale for these maneuvers to displace the mandible. 2. The modifications for infants and children are different from the procedures used on adults. 3. Insertion of the thumb in the mouth during practice is frequently distasteful. 4. Both methods are impractical and often impossible to demonstrate and practice effectively on conscious volunteers. The practice victim often cannot relax his chest or keep his glottis open. He cannot relax his jaw muscles to allow forward displacement, which may be quite painful. 5. The instructor cannot evaluate whether trainees have learned these procedures.

Head-Tilt Oral Resuscitation

Advantages.—All of the objections to the previous techniques have been overcome with the head-tilt method of resuscitation, particularly when first preference is given to the nasal route of inflation of the victim's lungs. Gastric inflation by this route is negligible or absent, apparently as a result of the resistance to airflow through the nose. Whether the nose or mouth is used, leakage is not a problem. During mouth-to-nose breathing, the victim's mouth is held closed. During mouth-to-mouth breathing, the rescuer presses his cheek against the victim's nostrils, if necessary, to prevent leakage. The same method is equally suited to the victim with the tight jaw, as illustrated by the successful mouth-to-nose case cited above. Despite trismus, the head can be tilted and this action opens the nasopharyngeal and glottic air passages.

The simplicity and ease of evaluating performance of the method are major advantages. Experience has shown that it can be taught and practiced in a few minutes, with minimal discussion of the anatomy of the air passages. It is easy for casual rescuers to remember the simple steps of tilting the head back as far as possible and inflating the lungs through the nose or mouth.

Performance.—Instructions for head-tilt oral resuscitation are as follows. 1. Lift the neck (fig. 1*A*). 2. Tilt the head as far back as possible by holding the crown of the head with one hand. (Sufficient tilting usually opens the victim's mouth.) 3. Pull the chin upward with the other hand (fig. 1*B*). (X-ray studies show this action produces a wider open air passage than that of normal conscious subjects.) 4. Inflate the lungs through the nose or mouth or, in an infant, through the nose and mouth (fig. 1*C*). 5. Remove your mouth to let the victim exhale passively (fig. 1*D*). (If necessary, let him exhale through his mouth by momentarily separating his lips.)

The position of the rescuer's hands and the wide area of the oral seal must be emphasized for successful performance of this method. Both the rescuer's hands continuously maintain maximum extension of the head (fig. 2, *left*). Nasal inflation is preferred, to avoid gastric dilatation. Inflation through the victim's mouth in the event of nasal blockage merely requires separation of his lips with the rescuer's thumb, which is already in place on the victim's chin (fig. 2, *center*). In babies and children care must be taken to pull the chin upward, without exerting pressure on the soft tissues, which could encroach on the air passages (fig. 2, *right*).

An important modification is the optional use of the semilateral position for the victim. The victim's shoulder may rest continuously on the rescuer's knee during resuscitation (fig. 3). From this position, the victim's head is easily tilted to provide gravity drainage of fluid from the pharynx (fig. 3, *inset*). Small victims, particularly after submersion in water or obstruction by a foreign body in the upper airway, should be inverted and, if necessary, sharp blows applied between the shoulder blades to help dislodge the offending material (fig. 4).

The head-tilt oral method fulfills the need for a simple and effective universal procedure for resuscitating children and adults. Maximum extension of the victim's head opens and keeps open the air passages by the simplest known maneuver, without involving insertion of the finger or equipment into the mouth.

Oral Resuscitation by Laymen Without Adjuncts

Confusion has arisen from the failure to make a distinction between casual and trained rescuers. It should be emphasized that methods of resuscitation available to the general public must be simple, safe, and easily learned and must require no adjunct.

A compilation of data in "Accident Facts," a booklet published by the National Safety Council, indicates that approximately 11,000 deaths per year occur as a result of asphyxia or suffocation.

Records for 1957-1958 indicate that two-thirds of initial resuscitation attempts are made by housewives or passers-by. Thus, the major criticism of adjunctive equipment for resuscitation is that these nonprofessional rescuers who account for the majority of rescues cannot be expected to have the adjuncts with them at all times and should not be encouraged to spend the time required to find them in an emergency. Specialized techniques involving equipment should be considered only for persons trained in (*a*) the management of the air passages and (*b*) artificial ventilation of the unconscious patient.

Another difficulty besetting the casual rescuer is that he cannot diagnose with certainty the level of reflex response of the unconscious patient. He will attempt artificial respiration in any apparently unconscious person. Methods which simply require contact with the face and inflation through the nose or mouth can do little harm under any circumstances. In contrast, the hazards of instrumentation of the throat of a semiconscious victim with an active gag reflex are laryngospasm or vomiting and aspiration. If rescue efforts involve manipulations in the pharynx, a victim of asphyxia is prone either to vomit or to regurgitate passively, with the resulting danger of acid stomach contents entering his lungs. Unlike the anesthetized, curarized volunteer, an asphyxia victim is not likely to have an empty stomach, has not received belladonna to diminish secretions and to suppress vagal reflexes, has not been depressed by anesthetic drugs, and has not been paralyzed by curare sufficiently to prevent retching and vomiting. Efforts at opening the mouth of a victim of asphyxia in the early stages are likely to be traumatic or to fail completely, since such victims have an interval of increased skeletal muscle tone, including trismus. Despite these difficulties, the nasopharynx or air passages around the teeth may well be available under these circumstances. Failure to use them promptly may result in failure of resuscitation.

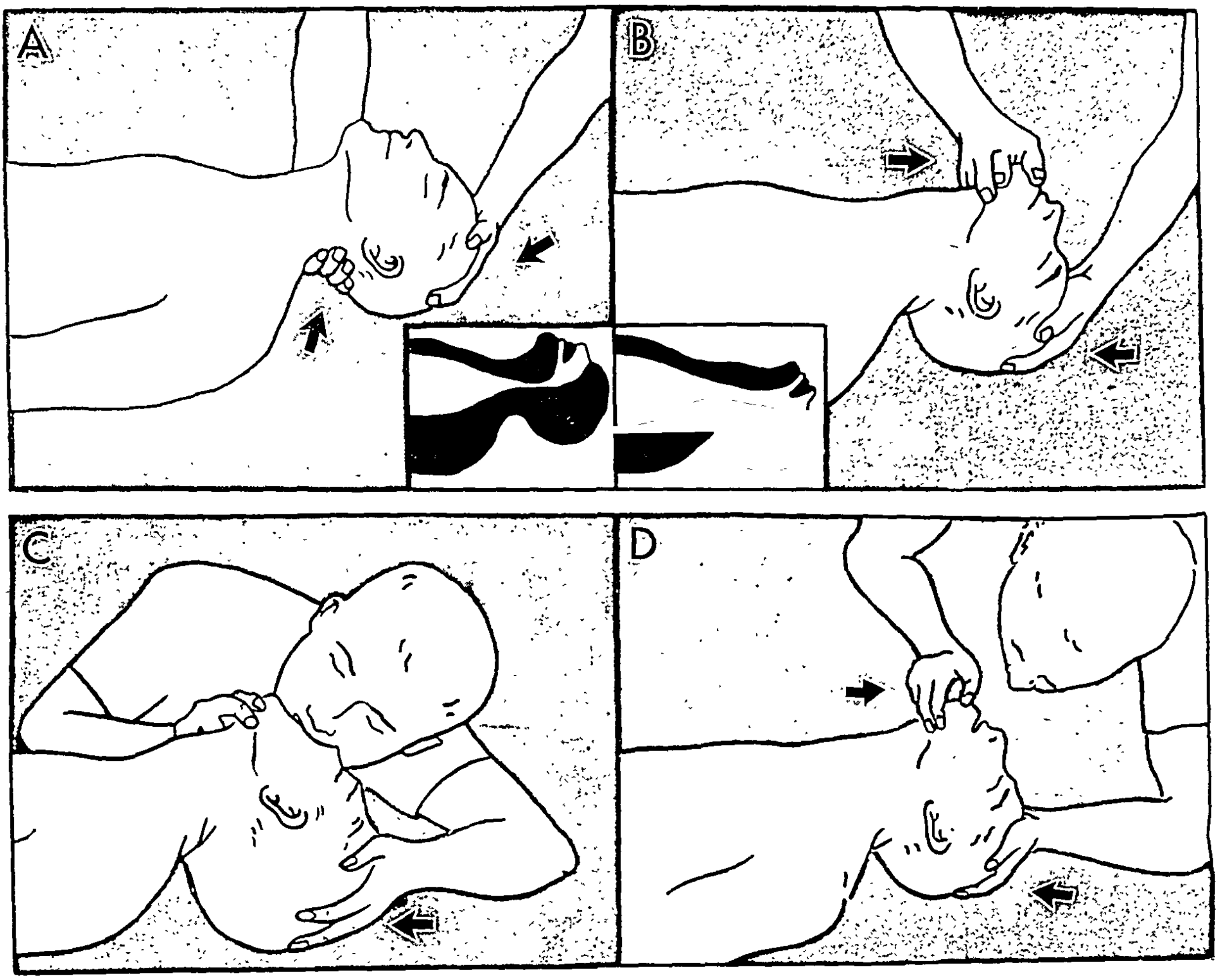

Fig. 1.—Head-tilt oral method. *A*, neck is lifted; *B*, head is fully tilted back; *C*, lungs are inflated via nose or mouth; and *D*, victim exhales by himself, if necessary, through his mouth.

Furthermore, considerable skill and experience are required in the proper use of the artificial oral airway, except in the deeply flaccid person. Experience is necessary, however, even then, to choose the right size to prevent trauma and to avoid pushing the tongue back to further block the air passages.

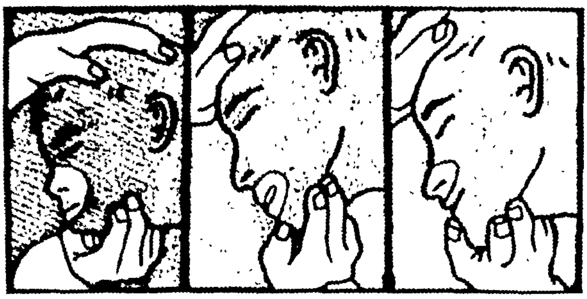

Fig. 2.—Wide area of seal around nose, mouth, or both: important detail in head-tilt oral method.

Since it is possible to prevent airway obstruction simply by maintaining the victim's head in the proper tilted position and employing either the oral or the nasal routes of inflation, commercial claims that resuscitation appliances work better than direct expired-air resuscitation lack substance in fact. In the seven reporting research centers, comparisons of efficiency and speed of resuscitation with and without adjuncts have repeatedly demonstrated the superiority of direct mouth-to-nose and mouth-to-mouth breathing by both professional and lay personnel. Furthermore, the use of any adjunct, even when it is readily available, causes delay in starting inflation of the lungs, even though this delay may be minimal. The several hundred successful resuscitations performed by laymen without adjuncts which have been reported in the last two years suggest that laymen will perform oral resuscitation without adjuncts.

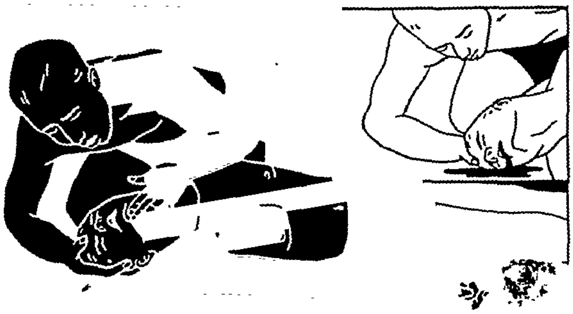

Fig. 3.—Semilateral position for gravity drainage of fluid from victim's oropharynx. Victim's shoulder should be pulled up on rescuer's knee. Gentle pressure should be used over epigastrium to facilitate emptying fluid from stomach.

Before the rescuer can safely use an oral airway in an emergency, he should understand how to test and to judge reflexes in patients after head injury, heart attack, convulsions, drug overdose, and electric shock. The layman who lacks experience in these emergencies should use the head-tilt method of oral resuscitation, with or without a handkerchief.

This head-tilt oral method of resuscitation fulfills the need for a universal method which opens the air passages and keeps them open by the simplest possible maneuver, does not involve insertion of the finger or equipment into the mouth, and is easy to teach and remember. It was officially adopted by the Holger-Nielsen committee of the Danish Red Cross, effective Oct. 7, 1959.

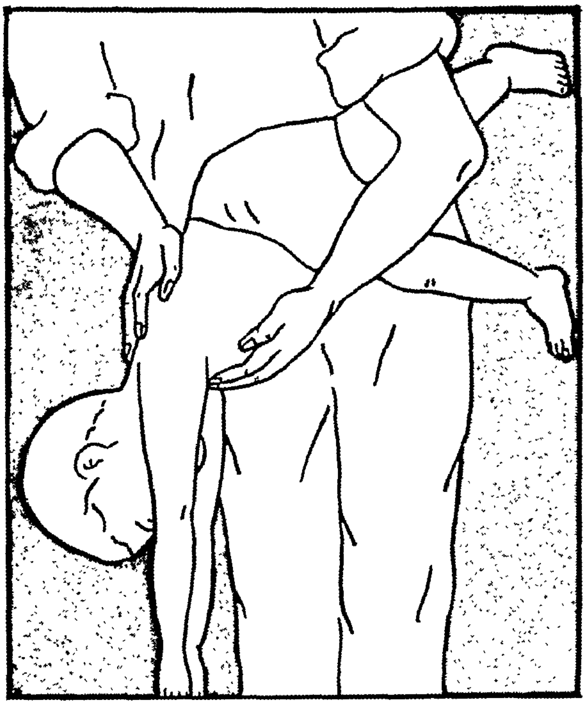

Fig. 4.—Method for dislodging obstructing material from child's throat. Victim should be inverted and sharp blow applied between shoulder blades.

Recently, the promotion and sale to the public of oral airways for resuscitation has been undertaken by commercial firms without official medical approval or the approval of organizations traditionally responsible for endorsement of methods of artificial respiration. We believe that (1) adjuncts (tubes and masks) should not be used by untrained laymen and (2) the head-tilt oral method, with use of the nasal or oral route of inflation, is the preferred technique to be tried first in all cases. The head-tilt method of oral resuscitation works better than any other field method of emergency artificial respiration, and, because of its simplicity, it is more easily learned than any other method.

CLINICAL NOTES

SPONTANEOUS RUPTURE OF THE SPLEEN AFTER ACUTE PANCREATITIS

REPORT OF A CASE

Robert H. LaBree, M.D., Josiah Fuller, M.D.
and
Paul G. Boman, M.D., Duluth, Minn.

In 1955, Byrd and Couch[1] reported a case of spontaneous rupture of the spleen with hemorrhagic left pleural effusion after pancreatitis. At laparotomy a huge hematoma had been found in the left upper quadrant of the abdomen. According to these authors, no previous similar case had been reported. In 1917, Turner[2] documented a case wherein splenic rupture, due to splenic infarct, was associated with hemorrhagic pleural effusion. In each instance, hemorrhagic left pleural effusion without previous injury to the thoracic cage was present.

An aftermath of acute, or recurrent, pancreatitis is the formation of many perisplenic adhesions which pull on the relatively mobile spleen and produce a shearing effect; this results in tearing of the soft, friable splenic tissue. In the patient we are reporting occupation may have played an important role; his job required driving a delivery truck over rough roads and repeatedly jumping in and out of the truck cab.

A 45-year-old man was admitted to St. Luke's Hospital on March 25, 1955, with complaints of constant pain in the left upper quadrant of the abdomen, weakness, belching, a 30-lb. (13.6-kg.) weight loss, anorexia, and dyspnea with fatigue on even slight exertion since November, 1954. The history was significant. The patient lived with his brother and cooked his own meals. The patient's brother and friends gave a history of heavy drinking by the patient. In November, 1954, the man had been under the care of another physician for persistent, sharp, and severe epigastric distress with radiation to the left upper quadrant of the abdomen and to the left flank. At that time, a serum amylase determination was reported to have been 456 units. A physical examination had revealed tenderness, guarding, and tympany over the entire upper part of the abdomen. The bowel sounds were said to be decreased. His physician at that time had believed the diagnosis to be acute pancreatitis. Compatible conservative therapy was started, and the patient improved, being discharged from his local hospital on Dec. 21, 1954. The attending physician later reported that at no time had an abdominal mass been palpable. In February, 1955, a cholecystogram was reported to have shown negative results. In March, the patient returned to his attending physician, complaining of pain in the left upper quadrant of the abdomen. One week later, the patient came under our observation.

Physical examination on March 25, 1955, revealed an extremely ill, pale, patient. Weight loss, weakness, and dyspnea were obvious. The examination of the abdomen revealed tenderness in the left upper quadrant. No mass was felt. The laboratory data showed the hemoglobin level to be 5 Gm. per 100 cc. (34%), the white blood cell count 14,250 per cubic millimeter, and the sedimentation rate 37 mm. per hour (Westergren). Further studies in the hospital indicated a lesion involving the left subphrenic space. Chest fluoroscopy and roentgenograms revealed elevation of the left part of the diaphragm, with immobility, plus definite evidence of a fluid collection in the left costophrenic sulcus. Aspiration of the fluid in the left side of the chest was not done.

Several days were spent correcting symptoms of dehydration and improving the general health of the patient. A preoperative diagnosis of rupture of the spleen associated with a left subphrenic hematoma, due to previous acute pancreatitis, was considered. On April 1, 1955, an operation was performed by way of a left subcostal incision. Exploration revealed a huge subphrenic hematoma on the left. After evacuation of the old blood, further search revealed a small pancreatic pseudocyst and indisputable evidence of recent fat necrosis. For several reasons, splenectomy was not performed and the abdomen was closed after two large Penrose drains had been placed in the left subphrenic space.

Recovery was slow but steady. In August, 1955, the patient returned to us with evidence of a large pancreatic cyst. On Aug. 31, 1955, this large cyst was marsupialized. The amylase level in the fluid obtained from the cyst at the time of operation was 1,900 units per 100 cc. Subsequent closure of the cyst was greatly facilitated by the use of an indwell-

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From the Department of General and Thoracic Surgery (Dr. LaBree and Dr. Fuller) and the Department of Internal Medicine (Dr. Boman), the Duluth Clinic.

ing catheter connected to a Stedman pump to drain the cyst and the administration orally of methantheline (Banthine) bromide to discourage pancreatic activity.

Since his recovery from the latter operation, the patient has had two episodes of mild but definite pancreatitis. These episodes necessitated hospital care; serum amylase values were found to be elevated in each instance. Presently, the patient is doing well and is allegedly avoiding the consumption of alcohol. Repeated roentgenographic studies of the gallbladder and gastrointestinal tract have revealed normal findings.

205 W. Second St. (2) (Dr. LaBree).

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CLINICAL SCIENCE

BLOOD NUCLEOTIDES

Charles Bishop, Ph.D., Buffalo

The statement is made frequently that uric acid is the end-product of purine metabolism in human beings. The serum level and urinary excretion of this compound have been extensively studied, particularly in patients with diseases such as gout, who show marked increases in urate levels. With the advent of chromatography and radioactive isotopes it has become possible to study some of the purine compounds that give rise to uric acid in the body. Because the purines are essential to life it is not surprising that these newer studies are touching many areas of medicine.

The body purines do not usually occur as free compounds but are ordinarily bound to molecules of sugar and phosphate. This combination of a purine such as adenine, a pentose sugar such as ribose, and phosphate is called a nucleotide. This particular adenine nucleotide is called adenylic acid, or adenosine monophosphate (AMP). More phosphates can be added to form the compounds adenosine diphosphate (ADP) and adenosine triphosphate (ATP). The various nucleotides are essential in energetics and as co-factors in many reactions. The nucleotides may also form copolymers with other nucleotides, some of which must be of the pyrimidine type. These mixed polynucleotides or ribonucleic acids (RNA) have a large molecular weight and a structure not unlike that of proteins. They are as essential to life as proteins and there is good evidence to suggest that they may furnish the templates on which protein molecules are synthesized. There is another type of nucleic acid which is formed from the nucleotides of "deoxy" sugars. This is that of deoxyribonucleic acids (DNA) which are found only in the nuclei of cells and from which the chromosomes are made. The purines (and pyrimidines) needed for synthesis of nucleotides and nucleic acids are derived from the diet either as preformed compounds or as simpler molecules from which the body can synthesize these nitrogen-containing ring systems. This latter process is called *de novo* synthesis.

The human red blood cell contains large quantities of nucleotides, particularly ATP. It had occurred to various investigators that these compounds might be direct precursors of the urinary uric acid excreted by human beings. I have studied some of these relationships, taking advantage of the fact that blood is an unusual tissue in that it can be maintained outside the body for several hours. Under proper circumstances in vitro its metabolism seems to be essentially that seen in vivo. For example, an aliquot of freshly drawn blood can be extracted with trichloroacetic acid and its nucleotides fractionated on columns of Dowex-1 formate resin.[1] Another sample of blood may be incubated at body temperature, under a suitable gas mixture, and after two hours its nucleotides can be extracted and fractionated in an identical manner. The two nucleotide patterns will be similar. This is not true for other tissue such as muscle or intestinal mucosa. It is difficult to carry out incubation studies on such tissues, as well as to determine their in vivo distribution of nucleotides, since the pattern deteriorates rapidly even during the short time needed to remove the tissue from the animal and immerse it in trichloroacetic acid.

We have incubated human blood with radiocarbon (C^{14})-labeled, preformed purines and have found that some of these purines are readily incorporated into the blood nucleotides. For example, adenine was promptly incorporated into ATP, while guanine was incorporated into the analogous guanine nucleotide, GTP. There was little interconversion of the purines, however. Furthermore, the uric acid of the blood did not become appreciably labeled. This suggested that the blood nucleotides, although active metabolically, were not major sources of blood uric acid. Another series of studies demonstrated that C^{14}-tagged glycine could not be incorporated into the human blood nucleotides. This indicated that these highly specialized cells did not synthesize purines *de novo.* The blood from gouty subjects was also studied, with use of the same incorporation and fractionation techniques. It was hoped that this might reveal some marked metabolic abnormality, such as *de novo* synthesis, which could account for the pathogenesis of gout. The gouty blood behaved almost like the normal blood, except that the data were less consistent. This suggested poorer regulation of purine metabolism in the gouty blood but did not point to any specific defect.

The mammalian red blood cell is unusual in that it carries on virtually no respiration. It derives its energy mainly from glycolysis, but some also comes from oxidation of glucose by way of the hexose monophosphate shunt. This is also called the pentose phosphate pathway, because several pentoses, including those excreted in pentosuria, can arise through the reactions involved. The first enzyme in this pathway is glucose-6-phosphate dehydrogenase. Through it the oxidation of [illegible] coupled to the reduction [illegible] nucleotide (TPN). It is the reduced TPN which presumably keeps hemoglobin in the reduced (active) state. Congenital or drug-induced methemoglobinemia is probably related to malfunction of the shunt pathway. This pathway is also involved in favism and in primaquine sensitivity, since the susceptible persons lack adequate amounts of the enzyme glucose-6-phosphate dehydrogenase. Under these circumstances they are unable to maintain adequate levels of reduced TPN (and thence reduced glutathione) when they come in contact with certain noxious substances. The exact relationships between hemoglobin reduction and hemolysis are not entirely clear as yet. Perhaps more than one mechanism is operating.

The viable red blood cell maintains a high concentration of potassium inside and a high concentration of sodium outside. This is paralleled by a high concentration of ATP in the cell. As the cell becomes less competent, the potassium begins to leak out and the sodium in, and the ATP concentration falls. These changes are reflections of failing metabolism and of a decreasing store of energy. Thus, the viability of stored red blood cells at a given time can be assessed by measuring the amounts and types of nucleotides present. By this means it is possible to compare various blood storage systems in a more quantitative way.

We have observed the blood nucleotide patterns of blood collected in A. C. D. solution and incubated at 37 C for periods up to three days. The changes are progressive and furnish a scale on which to measure blood stored under other conditions. It will be necessary to relate the blood nucleotide content of transfused red blood cells to their fate in the recipient, since this is the criterion of success in transfusion.

The determination of blood nucleotides for clinical purposes is now only in the research stage because of the time and skill required; nevertheless, some correlations have emerged. We have noted, for example, that, in patients with terminal nephritis, the blood nucleotides are dramatically increased.[2] Gouty patients exhibit some of these increases, although to a lesser extent. This suggests altered kidney function in the gouty subject and raises the question whether the gouty subject has primary or secondary kidney damage.

Other reports in the literature suggest that in hyperthyroid persons the blood ATP concentration is decreased.[3] One interpretation of these findings is that thyroid hormone interferes with the production of ATP or causes its more rapid dissipation. Drugs such as dinitrophenol are known to "uncouple" oxidative phosphorylation, and their thyroid-like activity may help to unravel the true action of thyroid hormone. Another report offers preliminary evidence that under certain conditions radioactive phosphorus is incorporated into ADP more rapidly in the blood of the schizophrenic patient than in the normal human being. Confirmation and extension of this finding may give a clue to the etiology of this disease.

It is apparent that uric acid, a compound in which great clinical interest has been shown for the past several decades, now has many chemical "relatives," some of which may be equally exciting. In the foregoing remarks I have attempted to highlight a few of the many possible interrelationships in this area and to suggest that potential clinical-biochemical relationships are awaiting their cues so that they too may give a memorable performance.

100 High St. (3).

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SPECIAL CONTRIBUTION

The following statement presented by President John S. Millis, of Western Reserve University, who served as Chairman of the ad hoc *Advisory Committee to the Committee on Scientific Activities of the Board of Trustees of the American Medical Association at the meeting held at Hershey, Pa., Sept. 14-16, 1959, is a résumé of the conclusions reached by this group. The thoughtful, constructive nature of this résumé merits widespread reading and consideration, and it is for this reason that the report is being published in* THE JOURNAL.

EDWARD L. TURNER, M.D., *Director.*

CHALLENGES AHEAD

John S. Millis, Cleveland

My task as Chairman of the *ad hoc* Advisory Committee is to review the scientific activities of the American Medical Association to describe the forest of which the individual trees have been described by my colleagues reporting on the deliberations of the five sections. In doing so I wish to acknowledge the assistance of each member of the Committee who contributed. It was clear that the members of the Committee are conscious of the fact that this is the first such conference convened by the A. M. A., and in that sense it has been a revolutionary occasion—an occasion in which we are trying to see how revolutionary forces can be channeled to produce evolutionary changes. We feel that the opportunity to learn more about the organization of the A. M. A. and to meet with representatives of the Board of Trustees, the Councils, Committees, Departments, and the staff has been a valuable experience. We are particularly grateful for the material that has been prepared for us and for the contributions that the A. M. A. staff has made to our discussions.

It is quite apparent that the American Medical Association has been reviewing its program during the past several years. We see every evidence of a critical and self-analytical approach to this review and we applaud the attitude which lies behind it. The American Medical Association has played a vital role in the development of medical education and medical science in the United States. We are conscious of the role of the American Medical Association in leadership in the advancement of medical education as personified by its role in the Flexner report. Since that study the A. M. A. has maintained a role of aggressive leadership in maintaining high standards for medical education and for medical science. In our deliberations we have been continually conscious of this position and have only desired to assure maintenance. The rapid changes that have occurred in medical education and medical science in the United States, particularly since World War II, raise intriguing challenges to any organization which is concerned with the maintenance of standards. It is our observation that the American Medical Association has been mindful of this problem and has kept pace with advances. Thus, we are not concerned primarily with past accomplishments but rather desire to look to the future.

It is my belief that in our considerations we have had an image expressed as to the fundamental nature of the American Medical Association. We see it as the greatest force, if not the exclusive force, within the fabric of medicine which is concerned with supplying unifying forces to be the counteraction to those forces which divide medicine itself. I have heard the words "umbrella" and "funnel" used and have dared to use the analogy of a cable-twisting machine or some sort of a device wherein you may unify many disparate and sometimes conflicting interests, forces, and energies under one single entity. The Association, therefore, has the same fundamental problem as any other organization within a free society which endeavors in a complex age, fraught with divisive forces, to produce coherence and unity. In itself, therefore, it must always be conscious of this unifying or "umbrella" function, and in all that it does, programwise and organization-wise, this should be a paramount consideration.

Relevant Ideas

To present the aspect before us, I would like to advance five central ideas which we think are relevant to the thinking and the planning and the action of the Division of Scientific Activities of the A. M. A.

Report of the *ad hoc* Advisory Committee to the Committee on Scientific Activities of the Board of Trustees of the American Medical Association, Hershey, Pa., Conference, Sept. 14-16, 1959.

People for Medicine.—I have called the first idea "people for medicine." The central problem of any learned profession or of any activity in life is the assurance of enough of the right kind of people for the continuation and for the health of the profession. Therefore, we must be concerned about students, and it is difficult for the consultants to see how the American Medical Association can forego a deep concern about the number of students coming to our medical schools and their quality. Suggestions have been made about plans for recruitment, and sometimes we take the defensive point of view on the plea that other professions are actively recruiting and soliciting students, frequently with an offer of financial assistance.

Second, it is a constant responsibility of the A. M. A. to insure that the health of the American people is adequately cared for with enough practitioners sufficiently efficient to discharge their responsibilities.

Third, frequent reference has been made to the necessity for seed-corn—those members of the profession who serve their roles as teachers and as investigators and who insure the future because they dedicate their lives and their energies to the teaching and to the investigative phase of the total profession.

And, last, I would enumerate under the general heading of "people for medicine" the continuing necessity for communication—communication from organized medicine to the young people of America so that they will know what the profession is and what its opportunities and its glories truly are; communication from organized education through the secondary, collegiate, and the graduate level; and communication to the general public about the people, who, after all, are the fundamental resource and asset of medicine.

Education for Medicine.—My second heading is "education for medicine." I believe it to be true in the entire educational process that it really has no beginning except birth and no termination except death, or perhaps in some cases retirement. But it is particularly true in the learned profession—I would remind you that medicine is one of the oldest worthy of that description—where there is an entire spectrum beginning with secondary education running through premedical preparation, through the full-time occupation of the student and the M.D. program, through the full-time occupation in the internship and residency, and through part-time occupation in continuing educational activities. This is a fragmented responsibility—part carried by secondary schools, part by colleges, part by medical schools, part by hospitals, and part by various associations and agencies in the continuing educational phase. No one in any organization is in so valuable and so central a position as to see the entire sweep of the educational process and to assume the responsibility for coordination and for relationship of that important thing which is education in medicine.

It should be pointed out, I think, in this connection, that since education is a vast sweep, when we think about the problems of support for education for medicine we cannot think in isolation about the needs of any single segment thereof but rather the entire spectrum of the process and the continuing process of education for medicine. Perhaps I might use this analogy: some foolish householder might be concerned exclusively with the condition of his house above the foundation line. He might spend vast sums in painting the exterior, in insuring the soundness of the plumbing or the weather-tight character of the roof, and fail to pay attention to the state of the foundation. I think the analogy is valid, for if medicine is concerned only about medical education as we normally think of it in the medical school or in the hospital, we are blind indeed, for the health of medical education is no greater than the total educational enterprise. As an example, unless the A. M. A. Division of Scientific Activities is as concerned about the sciences of chemistry, biology, physiology, and biochemistry as it is about the departments of surgery, psychiatry, pediatrics, and medicine, then it is neglecting an integral part of the total structure.

Interprofessional and Intergroup Relations in Medicine.—Third, I would direct your attention to the general heading of "interprofessional and intergroup relations in medicine." Medicine is fragmented. It is fragmented by specialization, but specialization is an absolute necessity; we shall have more of it and it shall be more intense. The physician will continue to be served by a vast array of groups in areas allied to medicine as he tries to multiply his effectiveness and his efficiency by having the assistance of many, many kinds of persons. Therefore, the relationship of these groups in areas allied to medicine—of specialty groups, of the teacher to the practitioner, the practitioner to the investigator—is of prime importance. The A. M. A. is the one organization which can do the most and, therefore, must carry the largest responsibility. In this might I express the hope that the A. M. A. would see this as a challenge and opportunity for a positive approach; for the A. M. A. must invite the interest and the association of these other groups. You cannot command it and they, being human, probably will not offer it voluntarily. There are perhaps things which the A. M. A. may do positively. One suggestion, which has not been made as a recommendation but is indicative of the thinking of some members of our group, concerns the idea of a group of medical scientists, advisory directly to the Board of Trustees, as an avenue by which the hopes, aspirations, goals, desires, and dreams of the medical scientists could be communicated directly to the top responsible body of the Association.

Inquiry for Medicine.—My fourth topic is "inquiry for medicine." I use the word inquiry rather than research or investigation because I think it includes both of those and more. As to the specific idea of research, Dr. Simeone, I think, has voiced the thinking of all of us that this is an area in which many other agencies are engaged and in which they have greater competence and greater skill, experience, and facilities than the A. M. A. has or could ever possibly have. This, on the other hand, does not mean that the A. M. A. does not have a responsibility and should not take the position of aggressive leadership. There is always the function of the review of research, the searching to identify and to see that gaps are filled in the whole process of medical research. There are various areas of direct inquiry—direct inquiry into the standards of medical care. As a university president, I am always conscious of the fact that when I try to exercise judgment on the recommendations of my colleagues of the faculty as to how medical education should be conducted, I do not have an authoritative and comprehensive statement from any competent and authoritative source as to what good medical care is, thereby to judge what good medical education shall be.

Another area of inquiry has been suggested, namely, some measurement of what it is that the practicing physician desires and needs in the field of continuing education. Hence, under the heading of inquiry for medicine, I would remind you of the evaluative function, the continual need for someone, some agency, or some organization to try to distill wisdom from information and knowledge from the compilation of statistical data. This function the A. M. A. is doing in the standards maintained for its journals, but it is a continuing responsibility.

Last, I would emphasize that single thread which runs through all of this, namely, the necessity for communicating ideas and thoughts and information and knowledge and, yes, even wisdom. This is something which an organization that assumes responsibility for providing coherence and unity cannot possibly escape. Communication in the field of inquiry, whether it be research or investigation is of fundamental and significant importance.

Philosophy of Organization for Medicine.—Fifth, I would mention philosophy of organization for medicine. If our image of what the A. M. A. wishes to be, is, and shall be in the future is correct, namely, a unifying force, then it seems to me that it follows directly and logically and inescapably that in the organizational techniques which the A. M. A. adopts to carry out its responsibilities, it must always and ever be careful to see that its organization is not divisive but always unifying. If we adopt the easy way of meeting problems by the organization of one more Division and one more Council as a universal technique, then we are introducing additional divisive forces and not doing what the A. M. A. wishes to do, namely, to provide unifying devices. It was for this reason that Group D, of which I was a member, spent so much time and I think emphasized so heavily the necessity of thinking about the organization of the Division of Scientific Activities in terms of universality with common techniques for the solution of problems—temporary, ephemeral, or long-term as they may be—and suggested that there is some merit at least in thinking about the possibility of an organization which reflects the common element and the uniting elements in this particular task.

Summary and Comment

May I now add a personal note, and I think I echo again the sentiments of all who have come here at your kind invitation—a sense of pleasure and a thankfulness for the opportunity of being together and trying to come to grips with knotty problems, but above all a sense of participation in a high adventure—the adventure of a group of men and women resolved to do a job against a background of freedom and liberty, of trying to meet the complex problems of our society with that context and upon those assumptions. The word which I would underscore and ask the A. M. A. always to have in its mind is that it is a *voluntary* association and that which is done is not done by the decisions of dictators or a single group of men or women but, rather, by the voluntary decision of a group of free men deciding that which is wise, prudent and moral, and thereby adjusting their own desires and needs, hopes and ambitions, and sometimes even their own economic circumstances, that this high purpose may be accomplished.

I hope that as the prosecution rests the case, at least as the *ad hoc* Committee rests its case, that we have perhaps accomplished something in response to your kind invitation.

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ACUTE PERIPHERAL ARTERIAL EMBOLIZATION

GUEST EDITORIAL

Richard W. Egan, M.D.

THE acute occlusion of a peripheral artery by an embolus poses a difficult problem in management for the internist and surgeon alike. The immediate mortality is disturbingly high. In this issue of THE JOURNAL, page 799, Goldowsky and Bowen report an immediate mortality of 37% in their series of 46 embolectomies in 42 patients. Andrus,[1] in 57 instances of peripheral arterial emboli treated without surgery, noted an immediate mortality of 32%. Rosenberg and associates[2] recently reported an immediate mortality of 10% after arterial embolectomy. Goldowsky and Bowen were able to obtain follow-up information on the 25 patients who survived the initial embolus. In this group there were nine late fatalities, and all but one could be attributed to cardiovascular disease.

The patient presenting with an acute occlusion of a peripheral artery poses a dual problem. The underlying cardiovascular disease from which the embolus arose is frequently of serious life-threatening proportions. These patients most commonly have rheumatic heart disease with abnormalities of cardiac rhythm, coronary artery disease with myocardial infarction, or extensive arteriosclerotic cardiovascular disease. The number of immediate and late deaths in this group of patients is for the most part directly proportional to the severity of their cardiovascular disease. The acute arterial occlusion is mainly a threat to the survival of the affected extremity, although it may contribute materially to the death of the patient. The consequences of acute embolic arterial occlusion vary with a number of factors. Occlusion of the anterior or posterior tibial artery of the leg or the radial or ulnar artery of the forearm often results only in transient pain and weakness of the extremity. On the other hand, practically all patients with a saddle embolus obstructing the bifurcation of the abdominal aorta will die if untreated. The ultimate effect of the occlusion of the arterial supply to an extremity is influenced by a number of factors. The survival or viability of the extremity distal to the occlusion is dependent on its collateral arterial supply. If this network is sufficient, the extremity will survive, although the sequelae of chronic arterial insufficiency may be anticipated. When marked proximal vasospasm and distal propagation of the clot is associated with the acute embolus, the collateral circulatory bed is impaired and progressive ischemia leading to necrosis will ensue.

There are three problems that confront the physician when caring for a patient with an acute peripheral embolic arterial occlusion, namely, the disease entity which caused the embolus, the arterial circulation of the affected extremity, and the prevention of subsequent embolic episodes. In that the deaths in these patients can frequently be attributed to the severity of their chronic cardiovascular disease and its progression, this should receive primary consideration in the treatment of the patient. If surgical embolectomy is contemplated one has time to evaluate the general status of the patient, particularly from the cardiovascular standpoint, and institute the indicated therapeutic measures. Furthermore, one has time to observe the effect of nonoperative therapeutic measures, such as sympathetic ganglion block or intra-arterial vasodilating agents, on the arterial circulation of the affected extremity. The acute occlusion is an immediate threat to the viability and survival of the affected limb. If sufficient collateral circulation is present to assure viability of the tissues distally, especially in the presence of serious decompensated heart disease, conservative nonoperative therapy aimed at augmenting the collateral arterial flow and preventing the propagation of the clot will often suffice. In view of the advancements in vascular surgery it is possible to ameliorate or correct the resulting chronic ischemia at a later time under less adverse circumstances. When the embolus is lodged in a major vessel with marked peripheral ischemia and insufficient collateral arterial flow, then a care-

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Assistant Professor of Surgery, University of Buffalo School of Medicine, Buffalo, N. Y.

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fully planned and executed surgical embolectomy to establish a more normal arterial flow is mandatory to increase the limb salvage rate. The high attrition after successful management of such an episode and the number of patients who have subsequent embolic phenomenon makes it necessary that intensive long-term preventative measures be instituted. This may mean valvuloplasty in some and probably long-term anticoagulant therapy in most patients.

Only by a combination of intensive medical therapy of the underlying disease, careful selection of patients for surgical embolectomy, and intensive, diligent, and prolonged preventive measures in the postembolic period will the immediate and late mortalities be reduced and the limb salvage rate increased. In the future the addition of human fibrinolysin for the dissolution of fresh thrombi may be a worthwhile addition to our therapeutic armamentarium.

URIC ACID SECRETION AND EXCRETION

The course that uric acid (urate) follows through the kidney has been the object of investigation since the development of techniques of the study of this function. The best evidence advanced a generation ago, in the golden age of physiology, suggested that plasma uric acid is completely filtered through the glomerular membrane, that a significant proportion of the filtered substance is reabsorbed by the tubules, and that none is excreted through active enzymatic mechanisms or by differences in osmotic pressure between the tubules and circulating blood. A. N. Richards, of the University of Pennsylvania School of Medicine, and Homer W. Smith, of New York University College of Medicine, were staunch proponents of this mechanism. Their conclusions were supported by the best experimental data available at that time produced by the best techniques that had been devised.

It was important to place reliance on a sound concept of the mechanism of exchange of uric acid in any consideration of the pathogenesis of gout. An acceptable working or proved hypothesis of renal exchange was vital to the explanation of the increased concentration of uric acid in blood and body fluids—a consistent abnormality in patients with gout. An increased concentration of plasma uric acid could be related to (*a*) impaired destruction resulting from a deficient enzyme system, (*b*) increased production of uric acid resulting from an overly active enzyme system or from a shunt mechanism in the intermediary metabolism of this substance, or (*c*) an abnormality in the renal excretion of uric acid resulting from either impaired filtration by the glomerular membrane or altered excretion through the tubules.

The destruction of uric acid in patients with gout is not an attractive hypothesis, nor has any laboratory evidence been produced to support this mechanism. The polemic over the years has been waged concerning the second and third possibilities. A limited number of patients with gout excrete abnormally large quantities of uric acid in the urine. Investigation by isotope techniques of another segment of the gouty population reveals an overproduction of uric acid. There remains yet a third segment of those afflicted with gout who reveal neither defect. The clinical findings of articular gout and an increased concentration of uric acid in the serum leaves no doubt about the diagnosis. The failure to discover a satisfactory etiological mechanism in this group has prompted reexamination and restudy of the renal exchange of uric acid in gouty and nongouty persons.

Studies of this function have been reported recently from two laboratories. Gutman and associates,[1] at the Mount Sinai Hospital in New York, presented experimental data in support of the mechanism of tubular secretion of uric acid in the normal as well as the gouty person, a reversion to the Heidenhain theory of renal exchange of solutes. Gutman's observations have led him to an additional premise, i. e., under normal circumstances, the uric acid excreted from the kidney and into the bladder is largely derived by tubular secretion. Nugent and Tyler,[2] of the University of Utah School of Medicine, administered urate precursors orally to nongouty subjects in order to increase their plasma uric acid concentrations to the range found in patients with gout. Under these conditions the urate clearance and urate excretion rates achieved in nongouty subjects were well above those observed in the gouty patients. Nugent and Tyler concluded that abnormal renal excretion of uric acid is one important cause of hyperuricemia in some patients with gout. Secretion of uric acid by the renal tubule seems likely on the basis of the investigations pursued in these laboratories, widely separated geographically.

It is reasonable to assume at present that the pathogenesis of gout may be a function of several metabolic abnormalities and may not be confined to a single defect. An increased formation of uric acid contributes heavily in some patients with gout; in others there may be an abnormal renal exchange to account for the increased concentration of uric acid in body fluids. All or a portion of the uric acid that appears in the bladder urine may be the result

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2. Nugent, C. A., and Tyler, F. H.: Renal Excretion of Uric Acid in Patients with Gout and in Nongouty Subjects, J. Clin. Invest. 38:1890-1898 (Nov.) 1959.

of secretion by the tubules and not the residual of reabsorption of filtered urate. Secretion of uric acid by the tubules also provides a satisfactory explanation for the hyperuricemic effect of two drugs, pyrazinamide and chlorothiazide, useful therapeutic agents with a hyperuricemic side-effect quite unrelated to their desirable therapeutic features.

The alteration in emphasis on the etiological mechanisms responsible for the changes observed in gouty patients does not modify the recommendations for treatment. The prophylactic value of colchicine and a potent uricosuric agent remains good. These drugs are practical and effective in the prevention of recurrences of acute articular distress.

AN OUTSIDER SPEAKS

Formal education in America has been fortunate over the years in attracting a select number of physicians to the post of president or chancellor of some of our great universities. The promotion to the top rung of the academic ladder has been through the deanship of the medical school in some instances; in other schools the advancement has been from the headship of a clinical or basic science department. From whatever source the talent is sought, performance has been notable and the university has reaped the reward of outstanding leadership. The majority of university presidents, however, have not been medically trained and have had no choice but to learn by conference and contact in a relatively short time about this one division of the university which is unique and different from all of the others. An example of uniqueness is the annual budget.

The financial burden imposed by a medical school on the parent university is a critical item that no university president can pass by readily. In return, the stature of the medical school and the enhancement thereby of stature of the university is an ill defined but highly desirable investment that no president dares ignore. Indeed several outstanding universities in America are better known for the medical schools in the eyes of the public than for any other department, fine as the other departments may be. Western Reserve University, an institution of higher learning, supports an excellent medical school as well as an excellent university in the broad sense of the term. John S. Millis is the president.

President Millis participated in the Hershey, Pa., conference which was held under the Division of Scientific Activities of the A. M. A. This was a notable conference and attracted many outstanding leaders in medical and liberal education in America. Several of the contributions have appeared in The Journal. In this issue a summary of the deliberations of the *ad hoc* Advisory Committee of the conference is published. The exposition by President Millis is clear, penetrating, and thoughtful. The position of the American Medical Association in medicine for tomorrow is presented imaginatively but not extravagantly, and no promise is offered that cannot be achieved if proper forces are permitted to operate. President Millis was not medically trained. There is no doubt, however, of his ability to comprehend the problems that face American medicine and how best to reach the goals that lie ahead.

This report is recommended reading. The conclusion bears repetition: "——a sense of participation in a high adventure—the adventure of a group of men and women resolved to do a job against a background of freedom and liberty, of trying to meet the complex problems of our society with that context and upon those assumptions. The word which I underscore and ask the A. M. A. always to have in its mind is that it is a *voluntary* Association and that which is done is not done by the decisions of dictators or a single group of men and women but, rather, by the voluntary decision of a group of free men deciding that which is wise, prudent, and moral—and thereby adjusting their own desires and needs, hopes and ambitions, and sometimes even their own economic circumstances, that this high purpose may be accomplished."

THE CONFERENCE

In effect, the conference has become, the world over, a substitute for the work. That is its appeal. Take at any instant a census of the great talents of the world and you will find the large proportion preparing, attending, or recovering from a conference. When you add to the burden of the physical event itself the mass of ancillary paper work required, from the preparatory letter writing to the transcripts of discussions that nobody reads (except to correct his own stammerings before publication), you may conclude that here make-believe reaches its apogee.—J. Barzun, The House of Intellect, New York, Harper, 1959.

CHANGE OF ADDRESS

If you change your address please notify The Journal at least six weeks before the change is made. Include the address label clipped from your latest copy of The Journal, being sure to clearly state both your old and new address. If your city has Postal Zone Numbers, be sure to include this Zone Number in your new address.

DEPARTMENT OF ECONOMIC RESEARCH

"THE CONSTITUTION OF LIBERTY"

Arthur Kemp, Ph.D., Chicago

It is a unique privilege and a delight to read for the first time a time-tested classic; it is an even rarer privilege to recognize a great book when first it is published. Such is "The Constitution of Liberty,"[1] intended to be published 100 years to the day after the first appearance of John Stuart Mill's essay, "On Liberty."

Fifteen years ago Professor Hayek warned eloquently of the trend of human events in western civilization in a volume entitled "The Road to Serfdom." Phenomenally successful, its impact on liberal thought can be credited with having dealt a mortal blow against the socialism then growing in England. Professor Hayek has now developed more fully a system of political and social thought dedicated to liberty and based on the thesis that only through liberty can the spirit of civilization survive. It provides the most significant contribution in the 20th century to a restatement of the principles of a free society on which the growth and even the survival of western civilization depends. It is not merely a statement of faith, although Professor Hayek's faith in freedom is apparent despite his conscious and evident attempt to bend over backward in avoiding the emotional connotations frequently associated with the terms freedom and liberty.

"The Constitution of Liberty" is a philosophical treatise consisting of three parts. The first concerns itself with the basic issues and values of liberal political and economic philosophy. The second describes the development of those institutions of western civilization that, up to the present, have helped to establish a relatively high degree of individual liberty; essentially it is a historical description of the development of classical liberal jurisprudence. The third part tests the principles espoused in the first part and the institutions described in the second by applying them to some of the critical economic and social issues of our times.

So far as basic philosophy is concerned, perhaps the most significant appeal to the medical profession is Professor Hayek's explicit recognition of the boundless variety of human nature, of the infinite variety of individual attributes, and of the wide range of differences in the capacities and abilities of individual human beings. This is the biological and, hence, medical cornerstone on which "The Constitution of Liberty" rests.

There are also passages of great interest to the medical profession in its current struggle against attempts by government to coerce and control that profession and the financing of medical care. Chapter 19 deals with the relationship of the principles of liberty to the problem of what is called social security, including provision for old age, unemployment, and sickness. Professor Hayek clearly recognizes that the term "social insurance" is in fact a misnomer. He points out that "from the beginning, it had little to do with insurance and has since lost whatever resemblance to insurance it may ever have had" (p. 289). He also warns with vigor of the dangers inherent in acceptance of the value judgments of the new expert in a particular institutional setup, who is, by definition, an expert simply because he is in favor of current trends in policy. This danger, Professor Hayek thinks, is particularly important in such areas as social security systems, housing, education, and, as a matter of fact, the entire social service bureaucracy. Wisely he points out that "this is indeed one of the factors which tend to make so many contemporary developments self-accelerating. The politician who, in recommending some further development of current policies, claims that 'all the experts favor it,' is often perfectly honest, because *only those* who favor the development have become experts in this institutional sense, and the uncommitted economists or lawyers who oppose are not counted as experts" (p. 291).

Another fundamental principle on which Professor Hayek's treatise rests is the recognition of the debt man owes to the developments that have taken place beyond conscious social control, developments that are the result of spontaneous forces of growth, that were unknown and perhaps unknowable. Hayek believes that the advantages of a free civilization have rested in the past, at least in part, on man's inability to control completely his social life; he is concerned lest, with a greater variety of controls within his power, man may hesitate to permit spontaneous development and perhaps may even discourage it by the use of controls, when in fact continued advance depends on his deliberately fostering spontaneity. "In the past," says Hayek, "the spontaneous forces of growth, however much restricted, could usually still assert themselves against the organized coercion of the state. With the technological means of control now at the disposal of government, it is not certain that such assertion is still possible; at any rate it may soon become impossible. We are not far from the point where the deliberately organized forces of society may destroy those spontaneous forces which have made advance possible" (p. 38).

This principle is recognized again and again throughout the book, perhaps nowhere more clearly than in the field of social insurance and, more particularly, health insurance. Hayek recognizes that governmental health insurance schemes have almost inevitably involved the development of a single-track government authority. The development of insurance was not dependent on the discovery of any single man or group of men; but the insurance principle evolved over time in a way that no man ever aimed at and no group of men created. His eloquent warning against state monopoly in these developments (p. 292) is as follows:

> Significantly enough, in the two main fields which the state threatens to monopolize—the provision for old age and for medical care—we are witnessing the most rapid spontaneous growth of new methods wherever the state has not yet taken complete control, a variety of experiments which are almost certain to produce new answers to current needs, answers which no advanced planning can contemplate. . . . To make the best available knowledge at any given moment the compulsory standard for all future endeavor may well be the most certain way to prevent new knowledge from emerging.

It might be an act of statesmanship as well as one of self-preservation to send marked copies of this book to all those members of Congress who are concerned with such legislative proposals as seem determined to halt the continuing development of private insurance in answer to health problems.

Hayek recognizes that it is not impossible to develop governmental allowances and social subsidy systems into systems of true insurance. He doubts, however, that there is as much to be obtained in this way as from those offered by competitive institutions and constant experiments with new ways of settling the questions.

Chapter 17, entitled "The Decline of Socialism and the Rise of the Welfare State," should be of great help to the members of the medical profession in understanding why it is much more difficult today to fight certain concepts of socialized medicine than it was when the attempt was being made to develop a complete and definite program of a new socialist society. Hayek believes the Marxist experience in Russia and the Socialist experience in Britain and elsewhere has brought about an abandonment of the traditional Socialist program. But, at the same time, this makes more difficult a defense against particular unsystematic collectivist actions that in and of themselves can be dressed up in very fetching garb. Even the attempt to designate such developments as the "welfare state" will not help since it is not in fact a recognized, organized system of thought. The defense of liberty is much more difficult when it is opposed by individual programs unconnected one with the other, such as Forand-type legislation and the like, than it is when the avowed purpose is to tear up the roots of existing society to establish a new one. The new, uncoordinated, piecemeal attack of the welfare state uses national coercive power "to insure that particular people get particular things, . . . a kind of discrimination between, and an unequal treatment of, different people which is irreconcilable with a free society . . . It is bound to lead back to socialism and its coercive and essentially arbitrary methods" (pp. 259-260).

One paragraph ought to be read by every member of the medical profession; indeed, by every member of every profession, and certainly by every statesman and politician. Hayek expresses it (p. 300) as follows:

> There are so many serious problems raised by the nationalization of medicine that we cannot mention even all the more important ones. But there is one the gravity of which the public has scarcely yet perceived and which is likely to be of the greatest importance. This is the inevitable transformation of doctors, who have been members of a free profession primarily responsible to their patients, into paid servants of the state, officials who are necessarily subject to instruction by authority and who must be released from the duty of secrecy so far as authority is concerned. The most dangerous aspect of the new development may well prove to be that, at a time when the increase in medical knowledge tends to confer more and more power over the minds of men to those who possess it, they should be made dependent on a unified organization under single direction and be guided by the same reasons of state that generally govern policy. A system that gives the indispensable helper of the individual, who is at the same time an agent of the state, an insight into the other's most intimate concerns and creates conditions in which he must reveal this knowledge to a superior and use it for the purposes determined by authority opens frightening prospects. The manner in which state medicine has been used in Russia as an instrument of industrial discipline gives us a foretaste of the uses to which such a system can be put.

If there were but one nonprofessional book every doctor could read in the year 1960, this ought to rank high on the list. It deals with the basic problems of freedom that are of paramount importance not only to medicine but to each and every person. Moreover, it will aid the members of the medical profession, and indeed all of us, to understand that the benefits of freedom are not confined to the individual doctor or to the medical or any other profession. We derive the greatest benefits not because we are free but because others are free. To recognize this is essential to an understanding of the nature of a free society and the benefits to be derived therefrom. Above all, in the struggle to survive in the war of ideas, we must recognize this principle as fundamental to our own position lest, as the saying goes, "we manage to snatch defeat even from the jaws of victory."

Reference

1. Hayek, F. A.: The Constitution of Liberty, Chicago, University of Chicago Press, 1960.

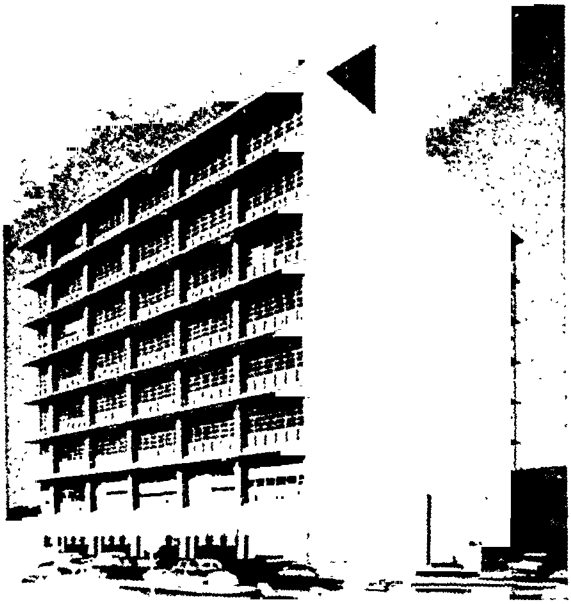
MEDICAL NEWS

DISTRICT OF COLUMBIA

Mental Health Bureau Appointments.—The Government of the District of Columbia, Department of Public Health, announced that on Jan. 4, Dr. David A. Lanham and Dr. Irving L. Berman joined the staff of the Legal Psychiatric Services Division. Dr. George Chornesky was appointed acting chief, Alcoholic Rehabilitation Division, effective Jan. 11, succeeding Dr. Jean H. Menetrez, who will continue to work with the bureau as staff psychiatrist in the Adult Mental Health Division on a part-time basis.

FLORIDA

Research Building to Be Dedicated.—The University of Miami School of Medicine will dedicate its new research building on March 3 in an outdoor ceremony at the Medical Center in Miami. The building, nine stories high and containing 90,000 square feet of space, provides laboratory facilities for all departments of the school. Construction took 18 months, and funds were obtained from the U. S. Public Health Service, from Dade County (Fla.), and from university sources. Dr. Robert B. Lawson, chairman, department of pediatrics, is general chairman for the dedication program; Mr. Hoke Maroon, Miami banker and president of the medical school council, is co-chairman. Guided tours through the building will be sponsored for civic and professional groups as well as for the general public.



University of Miami School of Medicine Research Building (university photograph by David Greenfield).

IDAHO

Cancer Conference in Boise.—The American Cancer Society, Idaho Division, will hold its annual cancer conference April 1-2 at the Hotel Boise, Boise. The program includes the following participants: Dr. John L. McKelvey, Minneapolis; Sol Silverman Jr., D.D.S., San Francisco; Dr. Murray M. Copeland, Washington, D. C.; Dr. Ian G. MacDonald, Los Angeles; Dr. Michael B. Shimkin, Bethesda, Md.; and Dr. Walter C. Lobitz Jr., Portland, Ore. Informal luncheon discussions will be held the afternoon of April 1. Dr. Shimkin will be the guest speaker at the dinner 7:30 p. m., April 1, presenting "Medical Mission to Moscow." Two panel discussions are planned, one each day.

KENTUCKY

New Health Building in Frankfort.—The State Department of Health's new home in Frankfort—the McCormack Memorial Health Building—was dedicated on Dec. 6. The ceremony honored a father and son whose combined services as Kentucky's first two health commissioners covered 64 years. They were Dr. Joseph N. McCormack, who became the state's first health commissioner in 1878 and served until 1912, and Dr. Arthur T. McCormack, who succeeded his father and was in office until his death in 1943. Governor A. B. Chandler was the speaker at the dedication. Dr. Russell E. Teague, Louisville, present commissioner of health, presided. The new building, scheduled for completion in February, was built at a cost of $2,750,000. It is so designed that two more floors can be added.

MARYLAND

Hospital Program to Celebrate Relocation.—On April 24, the medical staff of the Sinai Hospital, Baltimore, will celebrate the relocation of its quarters by holding a scientific meeting at the new hospital. The program includes presentations by the following: Dr. Edward C. Curnen Jr., Chapel Hill, N. C.; Dr. Clarence Dennis, New York City; Dr. Saul J. Farber, New York City; Dr. Louis M. Hellman, New York City; Dr. Simon Koletsky,

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Cleveland; Dr. J. Stauffer Lehman, Philadelphia; Dr. Morton L. Levin, Buffalo, N. Y.; Dr. Irving M. London, New York City; and Dr. Franz Reichsman, Rochester, N. Y. Recently the hospital was moved from its original site in Southeast Baltimore to a new site in the Northwest section of the city. The new facility contains an increased number of beds and bassinets, including 119 ward beds, larger quarters for the School of Nursing, and an outpatient department designed to handle up to 100,000 visits per year. Residence buildings for nurses and house staff adjoin the hospital. A three-floor research building has been provided.

MICHIGAN

Researchers Win Psoriasis Award.—The department of dermatology, Baylor University College of Medicine, Houston, Texas, announced that Isadore A. Bernstein, Ph.D., Walter D. Block, Ph.D., Dr. Espey F. Cannon, Herbert H. Cornish, Ph.D., Dr. Arthur C. Curtis, and Dr. Walker A. Lea, of the department of dermatology, University of Michigan, Ann Arbor, have been awarded the third annual Mr. and Mrs. J. N. Taub International Award for Research in Psoriasis. The $1,000 award was given for their research presented in a series of papers published in the *Journal of Investigative Dermatology*, "Nitrogen Balance and Sulfur Excretion Studies in Psoriasis," "Serum Uric Acid Levels in Psoriasis," and "Distribution of Lipids and Free Amino Acids in Psoriatic Scales." This award was established by Carol and Henry J. N. Taub in honor of his grandparents.

MISSOURI

Dr. Moore Lectures.—The 13th Jack H. Tritt Memorial Lecture of the Jewish Hospital of Saint Louis was given Feb. 4 by Dr. Carl V. Moore, Busch Professor of Medicine and chairman of the department of medicine, Washington University School of Medicine, entitled "The Metabolism of Iron."

NEW YORK

Course on Electron Microscope Techniques.—A special summer laboratory course in techniques and applications of the electron microscope will be offered to qualified senior biologists and medical research workers under the direction of Prof. Benjamin M. Siegel at Cornell University's Electron Microscopy Laboratory. The session will run from June 13 through July 1. The course will include laboratory work, lectures covering the basic principles and methods, and lectures on specific biological applications to be given by guest lecturers. It is being sponsored by a grant from the National Science Foundation. Requests for information and applications should be addressed to Professor Siegel at Rockefeller Hall, Cornell University, Ithaca, N. Y.

New York City

Symposium on Chronic Alcoholism.—The National Vitamin Foundation, Inc., announced that on March 1 the annual meeting and symposium, "Complications of Chronic Alcoholism—Their Causes, Management and Prognoses," will be held at the Hotel Pierre. The morning session, which will be given over to discussion of the central nervous system complication of alcoholism, will be chaired by Dr. Joseph M. Foley, chairman, department of neurology, Seton Hall University College of Medicine. Dr. Charles S. Davidson, Thorndike Memorial Laboratory, Boston City Hospital, will be chairman for the afternoon discussion of the hepatic complications of chronic alcoholism. For information, write the National Vitamin Foundation, Inc., 149 E. 78th St., New York 21.

Personal.—Dr. Blaise A. Pasquarelli, psychiatrist, received a Fordham Alumni Association Award at the association's 106th annual dinner Jan. 26. The awards are given to alumni "for winning distinction for themselves and for their college through their professional accomplishments." Dr. Pasquarelli teaches psychiatry at the Columbia University College of Physicians and Surgeons and is doing research on "Psychoanalysis and Religion" and "Unexplored Sources of Anti-Semitism."——Dr. Alfred P. Fishman, associate professor of medicine, Columbia University College of Physicians and Surgeons, was elected a member of the board of directors of the New York Heart Association. Dr. Fishman has been chairman of the Scientific Program Committee of the association since 1957.——Dr. S. Charles Franco was recently appointed executive director of the medical department, Consolidated Edison Company of New York, Inc. Dr. Franco is a member of the board of directors of the Industrial Medical Association and is also associate professor of industrial medicine at the New York University-Bellevue Medical Center.

OHIO

Annual Anesthesiology Address.—Dr. Julius H. Comroe Jr., of the Cardiovascular Research Institute, University of California Medical Center, will be the guest speaker at the fourth annual Rolland J. Whitacre Memorial Address sponsored by the Cleveland Society of Anesthesiologists. This will be a dinner meeting at the Wade Park Manor Hotel, Cleveland, on Wednesday, March 9. For reservations, contact Dr. June A. Dvorak, secretary-treasurer, 2235 Overlook Rd., Cleveland Heights 6, Ohio.

List of Scientific Periodicals.—The Cincinnati Chapter of the Special Libraries Association has published a new Union List of Scientific and Technical Periodicals of the Libraries of Greater Cincinnati and Vicinity which is available for sale. The

Union List covers the holdings of 35 libraries to January, 1958. Orders for copies should be sent to Roberta Andrews, U. S. Public Health Service, Occupational Health Field Headquarters, 1014 Broadway, Cincinnati 2. Cost per copy, $10, is payable to the Special Libraries Association, Cincinnati Chapter.

Personal.—The Cleveland Clinic announced the appointment of Dr. Wallace B. Hamby to the staff of the department of neurological surgery. Dr. Hamby will assume his clinic duties July 1 after completion of the academic year at the University of Buffalo Medical School, where he has been professor of neurological surgery since 1941.——Governor Michael V. DiSalle reappointed Dr. Ralph E. Dwork, Columbus, associate professor of preventive medicine at Ohio State University, as director of of the Ohio Department of Health, effective Nov. 8. Dr. Dwork, first appointed in 1954, will again serve a five-year term.

OKLAHOMA

Outbreak of Diphtheria.—The Oklahoma Health Bulletin for January reported that a 10-year-old Chickasha boy was the first death of six diphtheria cases which occurred in a two-week period. A 52-year-old Boswell woman and a 16-year-old Kingston girl also died. In Vinita a boy, 6, recovered, and in Owasso a 16-year-old girl is recovering. A 3½-year-old boy and 33-year-old woman, both of Oklahoma City, reported as cases had not been confirmed. As of Dec. 15 cases in Oklahoma numbered 11 for the year. Dr. Grady F. Mathews, commissioner of health, said "So far we have sent out enough toxoid of various kinds to immunize 27,155 persons. It has gone to Chickasha, Stillwell, Hugo, Pauls Valley, Anadarko, Ponca City, Blackwell, Guymon, Idabel, Watonga, Duncan, Elk City, Pryor, Okmulgee, Dewey, Lawton, Eufaula, Madill, Jay, Vinita, Ardmore, Tishomingo, and Oklahoma City."

GENERAL

Executive Director for Health News Institute.—The appointment of Mr. Marc Woodward as executive director of the Health News Institute was announced by Dr. Austin Smith, president of the organization. The institute has offices at 60 E. 42nd St., New York 17. Dr. Smith, Washington, D. C., president of the Pharmaceutical Manufacturers Association, said Mr. Woodward succeeded Mr. Chet Shaw, who resigned. Mr. Woodward has served as assistant executive director of the HNI since 1956, when the institute was organized.

Grants Available for Blindness Research.—The Research Committee of the National Society for the Prevention of Blindness invites requests for research grants in 1960. Funds are available for projects that may "contribute to basic understanding of eye function and pathology, or that may improve methods of diagnosis, treatment, or prevention of blinding eye diseases." Grants will be made this spring for requests received by April 1. Inquiries may be addressed to Research Committee, National Society for the Prevention of Blindness, 1790 Broadway, New York 19.

Medical Genetics Course.—A short course in medical genetics (Heredity and Disease in Man and Animals) will be conducted at Bar Harbor, Maine, Aug. 8-20, by members of the faculty of the Johns Hopkins University School of Medicine, Baltimore, and the staff of the Roscoe B. Jackson Memorial Laboratory, Bar Harbor. Forty participants can be accommodated. The course is designed primarily for persons in medical teaching and research. Information can be obtained from the co-directors of the course: Dr. Victor A. McKusick, Johns Hopkins Hospital, Baltimore 5, and John L. Fuller, Ph.D., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine.

Fellowships for Connective Tissue Research.—The Helen Hay Whitney Foundation announced that fellowships are available to any qualified person in the United States or abroad, up to the age of 25, holding the degree of M.D., Ph.D., or equivalent, who is seriously considering a career in biological or medical research, preferably relating in some way to connective tissue and its diseases. Fellowships are annual, subject to renewal consequent to good performance for a period of three years. The stipend is $6,000 a year, plus $500 for each dependent. Applications must be received on or before Aug. 15. Address inquiries to the Helen Hay Whitney Foundation, 525 E. 68th St., New York 21.

Report on Accidents.—More people died in accidents in 1959 than in the preceding year, it is reported by statisticians of the Metropolitan Life Insurance Company. Accidents took about 91,500 lives in continental United States last year, the statisticians estimate. However, the accident death rate, reflecting the increase in population, declined fractionally for the fourth year in a row to an all-time low of 52 per 100,000 population. Motor vehicle accidents continued to be the major cause of fatal injuries, accounting for two-fifths of all accidental deaths. Such accidents were responsible for the loss of about 37,500 lives, or about 500 more than in 1958. Data currently available indicate that the motor vehicle accident death rate per 100 million vehicle miles in 1959 was slightly less than the all-time minimum of 5.6 established a year earlier. Public accidents other than those involving motor vehicles accounted for nearly 17,000 deaths last year, or about 500 above the 1958 toll. Accidents in and about the home killed 27,000 the same number as the year before, and accidents arising out of and in the course of employment resulted in about 13,000 deaths.

Allergy Meeting in Miami Beach.—The 16th congress and graduate instructional course in allergy of the American College of Allergists will be held Feb. 28-March 4 at the Americana Hotel, Bal Harbour, Miami Beach, Fla. The instructional course, conducted Feb. 28 through March 1, will be presented under the following major titles: Primary Considerations of Some Aspects of the Field of Allergy, Clinical Applications to Present Day Knowledge in Allergy, and Progress in Allergy: The Allergist of Today and Tomorrow. Dr. Ethan Allan Brown, of London, England, present director, Asthma Research Foundation, Boston, will present "Enzymes in Allergy" March 1. Dr. James H. Putman, president, Florida Allergy Society, will open the general scientific session, March 2 followed by an address by Dr. Cecil M. Kohn, president of the American College of Allergists. Sectional meetings for pediatric allergy, technology, psychosomatic medicine, dermatologic allergy, and allergy of the nervous system are planned for March 4. Scientific exhibits are planned. For information, write the American College of Allergists, 2049 Broadway, Boulder, Colo.

White House Conference Publications Available.—The White House Conference on Children and Youth, scheduled for March 28-April 1 in Washington, D. C., has announced the availability of publications for use in the states in preparing for and following up the activities of the conference itself. The following publications are available at the prices listed, which include postage:

"The Nation's Children" (3 volumes)	$6.50 the set
"Children in a Changing World"	1.50
State Reports Digest	1.75
National Organizations Digest	1.75
Conference Proceedings	2.50
All the Above in One Order	11.30

The price offers listed above terminate as of March 26 and no assurance can be given that publications will be available at these prices thereafter. A descriptive flyer of the publications for distribution to memberships of state and national organizations is available. Requests should be addressed to Miss Helen Hamer, Publications Division, White House Conference on Children and Youth, 330 Independence Ave., S. D., Washington 25, D. C. Information is available from the same source.

College of Nutrition.—Formation of the American College of Nutrition was announced Oct. 26 by a group of New York and New Jersey specialists in nutrition, metabolic diseases, and gastroenterology. The college will not be limited to physicians in these fields but will include gerontologists, endocrinologists, surgeons, and others. Its purpose is to promote postgraduate research and education in therapeutic nutrition. The college is incorporated as a nonprofit organization subject to American Medical Association regulations. Its annual meeting will precede the A. M. A. convention in the same city each year, with the first meeting scheduled for Miami, Fla., in June. Dr. S. William Kalb, of Newark, N. J., was elected president of the new college. Dr. Kalb is chairman of the nutrition committee, Essex County Medical Society. Physicians eligible for fellowship are those whose professional activity is chiefly concerned with metabolism and nutrition and others in which nutritional or metabolic factors are important, including postoperative convalescence. Both fellowships and associate fellowships will be granted by the college. The administrative office of the organization is at 10 Oak Street, Livingston, N. J.

Award for Research in Accident Prevention.—The National Safety Council announced the Metropolitan Award for Research in Accident Prevention. One thousand dollars and an appropriate testimonial will be given for the research project in any field of accident prevention judged to be the "most significant contribution toward the reduction of accidental injuries and deaths." The award will be made "to give recognition to investigators now studying the causes of accidents to encourage research workers in the various sciences to include the problem of accident causation in their studies." Research may come from any of the various disciplines, i. e., biological, physical, or social, and can include interdisciplinary undertakings. Research may be submitted by the investigator, may be invited by the National Safety Council Committee on Research and Education, or may be nominated by anyone familiar with a research project. For information, write to Mr. John J. Flaherty, Director, Research Division, National Safety Council, 425 N. Michigan Ave., Chicago 11. This award, approved by the Executive Committee of the Board of Directors of the National Safety Council in October, 1959, will be administered by the Council under a grant from the Metropolitan Life Insurance Company.

Scholarships for Work with Crippled Persons.—For qualified persons wanting to further their training and to "better equip themselves" in working with the crippled, a new group of fellowships and scholarships are available, the National Society for Crippled Children and Adults announced. March 14 is the deadline for filing applications for 20 fellowships in counseling and job placement of the cerebral palsied and those having other physical handicaps, and April 1 is the deadline for scholarship applications for physicians, therapists, educators, and other professional persons working with children and adults having cerebral palsy. Fellowship awards are co-sponsored by the National Society and Alpha Gamma Delta, International Women's Fraternity. They cover four weeks of specialized training from June 13 to July 8 at the Institute of Physical Medicine and Rehabilitation of New York University–Bellevue Medical Center. The fellowships ($300 to be used for tuition and laboratory fees with the balance applied toward living expenses) are available to counselors and placement workers. Scholarships, co-sponsored by the national society and Alpha Chi Omega, are designed "to make more trained specialists available for serving the cerebral palsied and to supplement and increase the skill and knowledge of those already working with these persons." Courses for which scholarships are granted must have primary emphasis on cerebral palsy and participation of a member of the American Academy of Cerebral Palsy or have the prior approval of members of this academy serving as counselors to the national society. Grants are given in varying amounts up to $750, depending upon the length and scope of the course and the availability of other financial aid. Eligible to receive scholarships are physicians and other medical specialists. Applications and information can be secured from the Personnel and Reporting Service of the National Society for Crippled and Adults, 2023 W. Ogden Ave., Chicago 12.

LATIN AMERICA

Meeting on Cancer Cytology in Mexico City.—The International Conference of Cancer Cytology will be held in Mexico City May 2-11 instead of in Madrid, Spain, Dr. J. Ernest Ayre, Miami, and Dr. Locke L. MacKenzie, New York City, announced on behalf of Dr. Sanz Ibanez, of Spain, president of the conference. The announcement followed a meeting of the medical and scientific consultants of the Cancer Cytology Foundation of America, Inc., co-sponsoring the conference with the Pan American Cancer Cytology Society, the National Cancer Institute of Spain, and other medical groups. Dr. Ayre and Dr. MacKenzie, who are respectively president and U. S. national chairman of the Pan American Cancer Cytology Society, stated the conference will meet jointly with the Pan American Medical Congress. The theme of the Pan American Association Congress will be "Inter-American Good Will through Medical Science." Official support of the congress has been assured by the Minister of Health for Mexico and other government agencies and scientific organizations. The International Cancer Cytology Conference will bring together, by invitation, authorities in cancer cytology, as well as heads of WHO and UNESCO, to discuss ways and means of making cytology tests available to people of all countries. For information, write Dr. Robert E. L. Nesbitt Jr., Secretary, U. S. Office, International Conference, Union University, Albany, N. Y.

FOREIGN

Seminar Congresses in Vienna.—The American Medical Society of Vienna announced its schedule of 1960 seminar congresses held in cooperation with the medical faculty of the University of Vienna. The congresses are presented in the following specialties: dermatology and syphilology, internal medicine, neurology and psychiatry, obstetrics and gynecology, ophthalmology, orthopedic and traumatic surgery, otorhinolaryngology, pathology, pediatrics, radiology, and surgery. From 5 to 11 seminar sessions are scheduled on each specialty beginning in January, February, or April and continuing through November or December. For information on the seminar congresses, write Dr. M. Arthur Kline, executive secretary American Medical Society of Vienna, 11, Universitatsstrasse, Vienna 1, Austria.

Meeting of British and Irish Surgeons.—The Association of Surgeons of Great Britain and Ireland, 47 Lincoln's Inn Field, London, W. C. 2, under the presidency of Prof. F. A. R. Stammers, will hold its annual meeting in Birmingham on Thursday, Friday, and Saturday, April 7-9. Papers on open heart surgery will be presented following a business meeting the morning of April 7, with "Ulcerative Colitis" the theme for papers on the morning of April 9. Demonstrations and discussions on special subjects will be arranged at four hospitals the afternoon of April 8. Films, scientific exhibits, and demonstrations are planned. The annual dinner will be held at the Queen Elizabeth Hospital. For information, write Mr. Charles G. Rob, Honorary Secretary, at the above address.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. March 16, 1960 and Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, June 21-22 and Sept. 7-8. Part II, Various Cities, April 26-27. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 21-23. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

Alaska:[*] On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

Arkansas:[*] *Examination and Reciprocity.* Little Rock, June 9-10 Sec., Dr. Joe Verser, Harrisburg.

California: *Written.* Los Angeles, March 7-10; San Francisco, June 20-23; Los Angeles, Aug. 22-25 and Sacramento, Oct. 17-20. *Oral and Clinical.* Los Angeles, March 6; San Francisco, June 19; Los Angeles, Aug. 21, and Los Angeles, Nov. 29. *Oral for Reciprocity Applicants.* Los Angeles, Mar. 5; San Francisco, June 18; Los Angeles, Aug. 20 and Nov. 19. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

Canal Zone: On Application. Acting Sec., Dr. B. K. Levin, Health Bureau, Balboa Heights.

Colorado:[*] *Reciprocity.* Denver, April 12. *Examination.* Denver, June 14-15. Sec., Dr. John B. Farley, 1612 Tremont Place, Denver 2.

Connecticut:[*] *Regular. Examination.* Hartford, Mar. 8-10. Sec., Dr. Stanley B. Weld, 160 St. Ronan St., New Haven. *Homeopathic. Examination.* Derby, Mar. 8. Sec., Dr. Ronald A. Davis, 38 Elizabeth St., Dover.

Delaware: *Examination and Endorsement.* Dover, June 12-14 and July 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

District of Columbia:[*] *Reciprocity.* Washington, March 14. *Examination.* Washington, June 13-14. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., N.W., Washington 6.

Florida:[*] *Examination.* Miami Beach, June 19-21. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

Georgia: *Examination and Reciprocity.* Atlanta, June. Sec., Mr. Cecil L. Clifton, 224 State Capitol, Atlanta 3.

Guam: *Subject to Call.* Act Sec., Dr. F. L. Conklin, Agana.

Idaho: *Examination and Endorsement.* Boise, July 11-13. Exec. Sec., Mr. Armand L. Bird, 304 Sonna Bldg., Boise.

Indiana: *Examination.* Indianapolis, June 22-24. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

Maine: *Examination and Reciprocity.* Brunswick, March 8-10. Sec., Dr. Daniel F. Hanley, Box 637, Brunswick.

Maryland: *Examination.* Baltimore, June 15-18. Sec., Dr. Frank K. Morris, 1215 Cathedral St., Baltimore 1.

Michigan:[*] *Examination.* Ann Arbor and Detroit, June 6-8. Sec., Dr. E. C. Swanson, 118 Stevens T Mason Bldg., Lansing.

Mississippi: *Examination.* Jackson, June. Sec., Dr. A. L. Gray, Old Capitol, Jackson 13.

Montana: *Examination and Reciprocity.* Helena, April 5. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

Nebraska:[*] *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada:[*] *Examination and Reciprocity and Endorsement.* Reno, March 8. Sec., Dr. G. H. Ross, 112 No. Curry St., Carson City.

New Hampshire: *Examination.* Concord. March 9-12. Sec., Dr. Edward W. Colby, 61 South Spring St., Concord.

New Mexico:[*] *Examination and Reciprocity.* Santa Fe, May 16-17. Sec., Dr. R. C. Derbyshire, 227 East Palace Ave., Santa Fe.

New York: *Examination.* Albany, Buffalo, New York City, Rochester and Syracuse, June 28-July 1. Sec., Dr. Stiles D. Ezell, 23 S. Pearl Street, Albany.

North Carolina: *Endorsement.* Raleigh, May 9. *Examination and Endorsement.* Raleigh, June 20-23. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

North Dakota: *Examination and Reciprocity.* Grand Forks, July 6-9. Sec., Dr. C. J. Glaspel, Grafton.

Ohio: *Reciprocity.* Columbus, April 5 and June 17. *Examination.* Columbus, June 16-18. Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

Oklahoma:[*] *Examination and Endorsement.* Oklahoma City, May 31-June 1. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

Oregon:[*] *Reciprocity and Endorsement.* Portland, April 14-16. *Examination.* Portland, July. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

Pennsylvania: *Endorsement.* Harrisburg, March 3. *Examination.* Philadelphia and Pittsburgh, July 5-7. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

Puerto Rico: *Examination.* San Juan, March 1-5. Sec., Dr. Herminio Mendez Herrera, Box 9156 Santurce.

Rhode Island:[*] *Endorsement.* Providence, March 24. *Examination.* Providence, April 7-8. Administrator of Professional Regulations, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

Tennessee:[*] *Examination.* Memphis, March 23-24. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis 3.

Texas:[*] *Examination and Reciprocity.* Fort Worth, June 20-22. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

Utah: *Examination.* Salt Lake City, July 6-8. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

Virginia: *Examination and Reciprocity.* Richmond, June 13-17. Address: Board of Medical Examiners, 631 First St. S.W., Roanoke.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Arizona: *Examination.* Tucson, March 18. *Endorsement.* Tucson, March 15. Sec., Mr. Herman E. Bateman, University of Arizona, Tucson.

Arkansas: *Examination.* Little Rock, April 21-22. Sec., Dr. A. W. Ford, Department of Education, Education Bldg., Little Rock.

Colorado: *Examination and Reciprocity.* Denver, March 2-3. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

District of Columbia: *Examination.* Washington, May 23-24. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., Washington 6.

Florida: *Examination.* Miami, June 4. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

Iowa: *Examination and Reciprocity.* Des Moines, April 12. Sec., Mr. Elmer W. Hertel, Wartburg College, Waverly.

Kansas: *Examination.* Kansas City, June 10-12. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

Minnesota: *Examination.* Minneapolis, April 5-6. Sec., Dr. Raymond N. Bieter, 165 Millard Hall, University of Minnesota, Minneapolis.

Nebraska: *Examination.* Omaha, May 3-4. Sec., Mr. R. K. Kirkman, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada: *Examination.* Reno, March. Sec., Dr. Kenneth C. Kemp, Box 9355, University of Nevada, Reno.

Oklahoma: *Examination.* Oklahoma City, April 15-16. Exec. Sec., Mrs. E. L. Haidek, 813 Braniff Bldg., Oklahoma City.

Oregon: *Examination.* Portland, March 5. Sec., Dr. Earl M. Pallett, State Board of Higher Education, Box 5175, Eugene.

Tennessee: *Examination.* Memphis and Nashville, March 23-24. Sec., Dr. O. W. Hyman, 62 S. Dunlap St., Memphis.

Texas: *Examination.* Austin, Houston and Galveston, June 20-22. Sec., Dr. Cornelia M. Smith, State Office Bldg., 201 East 14th St., Austin.

Washington: *Examination.* Seattle, July 13-14. Administrator, Mr. Thomas A. Carter, Department of Licenses, Capitol Bldg., Olympia.

Wisconsin: *Examination.* Madison, April 9. Milwaukee, June 4. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

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[*] Basic Science Certificate required.

GOVERNMENT SERVICES

AIR FORCE

Medical Service School.—The Gunter Branch of the School of Aviation Medicine was redesignated the Medical Service School. It was originally established in 1950 to meet the training requirements of medical personnel during the Korean conflict. The present mission of the school is to conduct all military medical training for officers and airmen except that which is directly related to aviation medicine; to provide the necessary administrative support and supervision for all personnel assigned or attached to the school; and to organize, equip, and train, on a continuing basis, a medical disaster assistance team. Thirty-six different courses are offered, 12 for officers, 10 for advanced or supervisory technicians, and 14 for apprentice-specialist airmen.

NAVY

Reserve Training Course.—A two-week active duty course in military medical training, previously scheduled to convene on March 7, will convene March 14, at the Naval Medical School, Bethesda, Md. The first week will be devoted to medical aspects of special weapons and radioactive isotopes, with particular reference to casualties from atomic explosions. The second week will be devoted to professional topics of concern to military medicine, including discussions on reserve medical programs of the Armed Forces. Naval Reserve Medical Department officers are eligible for this course. Quotas have been authorized to commandants of the First, Third, Fourth, Fifth, Sixth, Eighth, and Ninth Naval Districts. Interested, eligible officers should submit a request for this training to their respective naval districts. Those who are ready reservists are eligible for active duty training with pay, and those who are standby reservists are eligible to participate in this training without pay.

PUBLIC HEALTH SERVICE

Assistant Surgeon General.—Dr. Arnold B. Kurlander, formerly deputy chief of the bureau of medical services, was named the assistant surgeon general of the Public Health Service. As assistant surgeon he is third in command. His specific area of responsibility will be to provide immediate staff assistance to the surgeon general on current program matters, to facilitate communications between the four bureaus of the service and the surgeon general's office, and to expedite the handling of program aspects of operating problems.

Water Pollution.—The water pollution control advisory board to the surgeon general met in January and recommended that (1) the Secretary of Health, Education, and Welfare support approval of a bill to increase grants for the construction of water treatment works, (2) the budget contain a separate item for water pollution control activities, (3) all federal and other public installations having waste disposal problems set an example to the rest of the country by better cooperation with state water pollution control agencies and the Public Health Service in installing needed waste treatment facilities, (4) the provisions of the Federal Water Pollution Control Act be strengthened to provide a more equitable mechanism for preserving and improving the quality of water supplies and that it be amended so that sources of pollution will not be exempt from the provisions of the act merely because of fortuitous geographical location, (5) additional cooperative state-Public Health Service basic data stations be established to provide information on the quality of our nation's water so as to enable states, localities, industries, and the federal government to protect public health and conserve water sources for public water supplies, propagation of aquatic life and wildlife, recreational purposes, and agricultural, industrial, and other legitimate uses, and (6) the enforcement provisions of the Federal Water Pollution Control Act be expanded to cover discharges from federal installations.

DEPARTMENT OF JUSTICE

Personal.—Dr. D. J. Lacovara was transferred from the Federal Correctional Institution, Ashland, Ky., to the Federal Correctional Institution, Lompoc, Calif., where he is chief medical officer and chief of the psychiatric service. This institution is a much-needed adjunct for those cases requiring 60 to 90 days of observation and study, pursuant to provisions of statutes designed to make available to federal judges more complete studies prior to imposition of final sentencing, with particular stress on the personality and mental status of the prisoner.

NATIONAL SCIENCE FOUNDATION

New Grants Brochure.—The January, 1960, revision of the National Science Foundation brochure, "Grants for Scientific Research," contains instructions for submission of proposals and information on administration of Foundation grants. Its terms become a part of all Foundation research grants. This revision contains new explanatory material on Foundation grant policies and some revisions of earlier instructions. Copies can be obtained from the National Science Foundation, Washington 25, D. C.

DEATHS

Abell, Charles Eckley Ⓜ Canton, Ohio; University Medical College of Kansas City, Mo., 1903; past-secretary of the Stark County Medical Society; died Nov. 7, aged 87.

Adams, Donald Vincent, Portland, Ore.; University of Oregon Medical School, Portland, 1958; interned at St. Vincent's Hospital; certified by the National Board of Medical Examiners; served a residency at the Physicians and Surgeons Hospital; died Dec. 4, aged 27.

Adams, Edwin Myron Ⓜ Red Lodge, Mont.; Medical College of Ohio, Cincinnati, 1909; health officer; died in Carbon County Memorial Hospital Dec. 4, aged 77.

Allen, Joseph Hugh Ⓜ Denton, Texas; Fort Worth School of Medicine, 1901; died Sept. 28, aged 81.

Allder, Alfred Eugene, Springfield, Mo.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1903; veteran of World War I; for many years city physician; died Nov. 7, aged 81.

Andrews, George Alvin Ⓜ Mount Gilead, N. C.; Medical College of Virginia, Richmond, 1929; died in the North Carolina Baptist Hospital, Winston-Salem, N. C., Nov. 11, aged 55.

Arford, Roxford Dennis Ⓜ Middletown, Ind.; Chicago College of Medicine and Surgery, 1911; veteran of World War I; on the honorary staff of the St. John's Hospital, Anderson, where he died Nov. 7, aged 73.

Auckley, Herbert Albert Ⓜ East Cleveland, Ohio; St. Louis University School of Medicine, 1925; served on the staffs of St. Ann Hospital and the Woman's Hospital in Cleveland, where he died Nov. 6, aged 60.

Baxley, William Ward Ⓜ Macon, Ga.; Medical College of Georgia, Augusta, 1927; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; past-president of the Bibb County Medical Society; senior chief of surgical service and past-president of the staff, Macon Hospital; past-president of the staff of the Parkview Hospital; associated with the Middle Georgia Hospital; died in Athens Nov. 14, aged 56.

Beckett, John Wesley, Memphis, Tenn.; University of West Tennessee College of Medicine and Surgery, Memphis, 1913; died in the Collins Chapel Hospital Dec. 1, aged 70.

Beckham, Louis Edgar Jr. Ⓜ Gadsden, Ala.; Medical College of Alabama, Mobile, 1947; interned at Jefferson-Hillman Hospital in Birmingham, Ala.; served a residency at the Georgia Baptist Hospital in Atlanta; member of the American Academy of General Practice; veteran of World War II; associated with the Baptist Memorial and Holy Name of Jesus hospitals; died Dec. 5, aged 33.

Bell, Charles Curry Ⓜ St. Paul; Rush Medical College, Chicago, 1919; died Oct. 9, aged 71.

Bell, Hubert O. Ⓜ York, Neb.; Northwestern University Medical School, Chicago, 1914; member of the American Academy of General Practice; associated with the York General Hospital, where he died Nov. 7, aged 73.

Bennett, Clayton Powers, New York City; Columbia University College of Physicians and Surgeons, New York City, 1890; died Sept. 7, aged 94.

Biddle, David H., Athens, Ohio; Medical College of Ohio, Cincinnati, 1895; died Dec. 6, aged 93.

Blaugrund, Charles Ⓜ Garfield Heights, Ohio; University of Lousiville (Ky.) School of Medicine, 1928; veteran of World War II; on the staffs of St. Luke's Hospital and Marymount Hospital; in charge of medical facilities for the Garfield Heights police and fire departments and the school system; died in the Marymount Hospital Oct. 31, aged 55.

Bloch, Jesse LeRoy Ⓜ Portugese Bend, Calif.; University of Oregon Medical School, Portland, 1919; member of the American Academy of General Practice; for many years practiced in San Pedro, where he was chief of staff at the San Pedro Community Hospital; died Nov. 15, aged 65.

Blome, Frederick Michael Ⓜ Champaign, Ill.; National Medical University, Chicago, 1906; died in the Carle Memorial Hospital, Urbana, Dec. 3, aged 79.

Bowers, Anderson Talbert Ⓜ Dayton, Ohio; University of Michigan Medical School, Ann Arbor, 1927; fellow of the American College of Surgeons; died Nov. 11, aged 58.

Boynton, Frances Nichols, Lockport, N. Y.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1903; for 27 years served in teaching and administrative positions at Arnold College, New Haven, Conn., and was assistant physician in the Arnold Orthopedic Institute; died Nov. 9, aged 91.

Ⓜ Indicates Member of the American Medical Association.

Brewington, George F., Las Vegas, Nev.; Ensworth Medical College, St. Joseph, Mo., 1892; veteran of World War I; died in Los Angeles Dec. 7, aged 96.

Brown, Charles Leonard Ⓜ Jersey City, N. J.; born in Metropolis, Ill., April 27, 1899; University of Oklahoma School of Medicine, Oklahoma City, 1921; specialist certified by the American Board of Internal Medicine; fellow of the International College of Surgeons and the American College of Physicians; member of the Central Society for Clinical Research, American Gastroenterological Association, and the American Society for Clinical Investigation; past-president of the Philadelphia County Medical Society, which in 1951 presented him with the Strittmatter Award; dean of the Seton Hall College of Medicine and Dentistry; professor of medicine at Temple Universtiy College of Medicine, Philadelphia, from 1935 to 1946; received the first annual achievement award, and from 1946 to 1955 dean of the Hahnemann Medical College and Hospital in Philadelphia, where he was head of the department and division of medicine; at one time on the faculty of Harvard University and the University of Michigan; member of the Revision Committee, U. S. Pharmacopeia XI, XII, XIII; the council of the American Pharmaceutical Association elected him a member of the Committee on National Formulary for a five-year term; in 1952 became a member of the council of chief consultants to the chief medical director, Veterans Administration in Washington, D. C.; formerly chief of the department of medicine, Philadelphia General Hospital; in 1951 received the honorary LL.D. from Temple University and in 1955 the honorary doctor of science from Hahnemann Medical College and Hospital in Philadelphia; died in the Jersey City Medical Center Dec. 4, aged 60.

Brumby, William M. Ⓜ Houston, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1889; past-president of the state board of health; at one time city health officer; member of the House of Delegates of the American Medical Association, 1909-1910; during World War II a member of the military service induction board; founder of the Texas Tuberculosis Association; died Nov. 29, aged 93.

Burkhardt, Edward W. Ⓜ Menomonee Falls, Wis.; Homeopathic Medical College of Missouri, St. Louis, 1896; died Dec. 7, aged 92.

Burnett, Alta Lawrence Ⓜ Durango, Colo.; Chicago College of Medicine and Surgery, 1908; fellow of the American College of Surgeons; associated with the Mercy Hospital; died Dec. 8, aged 74.

Butterman, Albert Ⓜ Chicago; Rush Medical College, Chicago, 1922; died Nov. 16, aged 67.

Callaway, Henry Abbott Ⓜ Maryville, Tenn.; Vanderbilt University School of Medicine, Nashville, Tenn., 1920; member of the Southeastern Surgical Congress; on the staff of the Blount Memorial Hospital; died Dec. 6, aged 64.

Campbell, Earl Henry Ⓜ Newberry, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1900; member of the American Psychiatric Association; specialist certified by the American Board of Psychiatry and Neurology; director of the Newberry State Bank; served as superintendent of the Traverse City (Mich.) State Hospital and the Newberry State Hospital; medical consultant to Tahquamenon Hospital, where he died Nov. 9, aged 81.

Campbell, Wayland E. Ⓜ Arlington Heights, Ill.; University of Arkansas School of Medicine, Little Rock, 1944; veteran of World War II; on the staffs of Sherman and St. Joseph's hospitals in Elgin; died Nov. 9, aged 46.

Canepa, Edward Gaten, St. Louis; Washington University School of Medicine, St. Louis, 1939; interned at St. Louis City Hospital; served a residency at the Glenwood Sanatorium in Webster Groves, Mo.; died Dec. 4, aged 44.

Capps, John Doak Ⓜ Livingston, Tenn.; University of Nashville Medical Department, 1908; past-president of the Overton County Medical Society; died Dec. 7, aged 75.

Carter, Charles Smith, Bells, Texas; Georgia College of Eclectic Medicine and Surgery, Atlanta, 1901; for many years a member of the state board of medical examiners; died in Sherman Dec. 8, aged 81.

Clark, Gorden Hay Ⓜ Belmont, Calif.; Hahnemann Medical College and Hospital of Philadelphia, 1949; member of the Industrial Medical Association; died near Beirut, Lebanon, Nov. 21, aged 48.

Coca, Arthur Fernandez, Oradell, N. J.; University of Pennsylvania Department of Medicine, Philadelphia, 1900; formerly on the faculty of Cornell University Medical College and New York Post Graduate Medical School in New York City; secretary-treasurer and served as honorary president of the American Association of Immunologists; for many years medical director of the Lederle Laboratories; founder and served as editor in chief of the *Journal of Immunology;* died in the Valley Hospital, Ridgewood, Dec. 11, aged 84.

Collins, Everett Naughtin Ⓜ Cleveland; Rush Medical College, Chicago, 1924; specialist certified by the American Board of Radiology and the American Board of Internal Medicine; member of the American Gastroenterological Association; fellow of the American College of Physicians; for many years on the staff of the Cleveland Clinic Hospital; died at his home in Cleveland Heights Nov. 6, aged 63.

Collmann, Xavier Kuehn Ⓜ Wilkes-Barre, Pa.; Medico-Chirurgical College of Philadelphia, 1916; fellow of the American College of Physicians; member of the honorary staff, Wilkes-Barre General Hospital; veteran of World War I; died in the Wilkes-Barre General Hospital Dec. 7, aged 69.

Cook, Raymond Joseph Ⓜ Lansing, Mich.; Loyola University School of Medicine, Chicago, 1935; member of the American Academy of General Practice; a staff member of Edward W. Sparrow and St. Lawrence hospitals; died Nov. 29, aged 53.

Cooksey, William Pate Ⓜ Magnolia, Ark.; University of Nashville Medical Department, 1899; past-president of the Columbia County Medical Society; died Nov. 23, aged 87.

Cooper, Linn Fenimore Ⓜ Washington, D. C.; born in Albany, N. Y., May 5, 1899; Harvard Medical School, Boston, 1926; interned at the Massachusetts General Hospital in Boston; served a residency at Johns Hopkins Hospital, Baltimore; for many years on the faculty of Georgetown University School of Medicine; at one time professor of medicine at Hsiang-Ya Medical College, Changsha, China; veteran of World War II; medical director, Washington Home for Incurables from 1936 to 1948; joined the Millhill Fathers Roman Catholic Mission, Kanowit, Sarawak; author of "Time Distortion in Hypnosis"; died in Sibu, Sarawak, on the Island of Borneo, Nov. 13, aged 60.

Culbertson, Roland Reed, Maud, Okla.; National University of Arts and Sciences Medical Department, St. Louis, 1912; veteran of World War I; died Dec. 6, aged 68.

Cunningham, Thomas J. Ⓜ Pine Bluff, Ark.; College of Physicians and Surgeons, Little Rock, 1910; associated with the Davis Hospital; died Dec. 8, aged 79.

Curtis, Charles Glenn Ⓜ Brea, Calif.; College of Medical Evangelists, Loma Linda and Los Angeles, 1924; veteran of World War I; at one time served with the government in South America for the Institute of Inter-American Affairs; member of the American Academy of General Practice; past-president of the California Public Health League and the Orange County Medical Society; died Nov. 15, aged 65.

Curtis, George Edmund, Altoona, Wis.; Manitoba Medical College, Winnipeg, Man., Canada, 1896; for many years practiced in Eau Claire; died Nov. 5, aged 92.

Daignault, Oscar Ⓜ Benson, Minn.; Laval University Medical Faculty, Montreal, Que., Canada, 1898; formerly member of the county board of health; fellow of the American College of Surgeons; served on the Swift County-Benson Hospital; died Nov. 18, aged 84.

Davies, Arthur J. Ⓜ Baltimore; Atlantic Medical College, Baltimore, 1910; on the staffs of the Maryland General and Lutheran hospitals; died in the Union Memorial Hospital Nov. 14, aged 73.

Davin, William Ambrose Ⓜ Hamilton, Ohio; University of Cincinnati College of Medicine, 1930; veteran of World War II; member of the American Academy of General Practice; member of the staff of the Mercy Hospital, where he died Nov. 7, aged 59.

Davis, James William Ⓜ Clinton, S. C.; Medical College of South Carolina, Charleston, 1895; veteran of World War I; died in Ponce de Leon Infirmary, Atlanta, Ga., Nov. 4, aged 89.

Dehm, Charles Henry, Middlegrove, Ill.; College of Physicians and Surgeons, Keokuk, Iowa, 1897; died in Elmwood Nov. 9, aged 91.

Devine, Hubert A. Ⓜ Fond Du Lac, Wis.; Marquette University School of Medicine, Milwaukee, 1918; fellow of the American College of Surgeons; past-president of the Fond du Lac County Medical Society; on the staff of St. Agnes Hospital, where he died Nov. 6, aged 66.

Downey, Martin Joseph Ⓜ Buffalo; University of Buffalo School of Medicine, 1899; for many years on the staff of the Emergency, Deaconess, and St. Francis hospitals; surgeon for the Erie Railroad; died Nov. 25, aged 83.

Dunham, Elgin Stephen Ⓜ Edmonton, Ky.; University of Louisville School of Medicine, 1931; member of the American Academy of General Practice; staff member of the T. J. Samson Hospital; died in Nashville, Tenn., Nov. 27, aged 55.

Dunne, George Michael, Balmorhea, Texas; University of Georgia Medical Department, Augusta, 1912; veteran of World War I; for many years health officer of Hudspeth County; died in Pecos Nov. 22, aged 78.

Ellis, Coburn Hudson Ⓜ Garden City, Mo.; University of Nebraska College of Medicine, Omaha, 1933; veteran of World War II; died in the Research Hospital, Kansas City, Oct. 25, aged 55.

Emmons, James Elmer, Island Pond, Vt.; University of Vermont College of Medicine, Burlington, 1933; veteran of World War II; certified by the National Board of Medical Examiners; died Nov. 11, aged 50.

Fauntleroy, Joseph Whittlesey, Saluda, N. C.; Medical College of Virginia, Richmond, 1893; Columbia University College of Physicians and Surgeons, New York City, 1896; died Dec. 4, aged 87.

Fennig, Foster Andrew Ⓜ Marquette, Mich.; Detroit College of Medicine and Surgery, 1932; veteran of World War II; in 1935 appointed prison physician of the Michigan State Branch Prison; on the staffs St. Mary's and St. Luke's hospitals; fellow of the American College of Surgeons; past-president of the Marquette–Alger Counties Medical Society; died Nov. 27, aged 58.

Flanagin, Wiley Monroe Ⓜ Waycross, Ga.; Atlanta School of Medicine, 1912; on the staff of the Memorial Hospital; past-president of the Ware County Medical Society; died Nov. 30, aged 80.

Fogelman, Hyman, New York City; Long Island College of Medicine, Brooklyn, 1927; died Oct. 29, aged 57.

Franklin, William Surman Ⓜ Scottsbluff, Neb.; Creighton University School of Medicine, Omaha, 1906; died Oct. 28, aged 79.

Freund, Newton M. Ⓜ St. Louis; Washington University School of Medicine, St. Louis, 1904; associated with the Incarnate Word, Jewish, St. Anthony, and Alexian Brothers hospitals; for many years on the staff of the Missouri School for the Blind; died in the Barnes Hospital Dec. 4, aged 76.

Frick, Walter Calvin, Braidwood, Ill.; Jenner Medical College, Chicago, 1908; served as mayor of Braidwood; past-president of the Reed–Custer High School board; died Nov. 23, aged 78.

Froelich, Erwin Christof Ⓜ Cleveland Heights, Ohio; Friedrich–Wilhelms Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1899; a German medical officer in World War I; died in Mount Sinai Hospital Oct. 31, aged 83.

Fry, Murdock De Witte Ⓜ Dallas, Texas; Baylor University College of Medicine, Dallas, 1922; member of the American Academy of General Practice; died in the Baylor University Hospital Dec. 2, aged 71.

Fuqua, Cleveland C. Ⓜ Hilliard, Fla.; Hospital Medical College, Eclectic, Atlanta, Ga., 1910; died Nov. 8, aged 70.

Ghrist, David Martin Ⓜ Glendale, Calif.; Keokuk (Iowa) Medical College, 1898; specialist certified by the American Board of Radiology; past-president of the Glendale Branch of the Los Angeles County Medical Society; associated with the Memorial Hospital of Glendale, where he died Nov. 14, aged 94.

Giddings, Charles G. Jr. Ⓜ Atlanta, Ga.; born in Atlanta Oct. 20, 1892; University of Virginia School of Medicine, Charlottesville, 1915; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians, of which he was ex-governor; clinical associate professor of medicine, Emory University School of Medicine; presented with the Crawford W. Long award for the best research work in the state during 1935-1936; veteran of World War I; attending physician, Emory University and Grady Memorial hospitals; consultant in internal medicine, U. S. Public Health Service; died in the Emory University Hospital Nov. 29, aged 66.

Gillespie, George Yancey Jr. Ⓜ Greenwood, Miss.; University of Virginia School of Medicine, Charlottesville, 1915; served on the staff of the Greenwood–Leflore Hospital; died Dec. 4, aged 68.

Glover, Charles Wesley, Cleveland; Loyola University School of Medicine, Chicago, 1916; veteran of World War I; on the staffs of the Grace and St. John's hospitals; died in Clearwater Beach, Fla., Dec. 5, aged 72.

Gran, Albert Godfrey, Storm Lake, Iowa; Northwestern University Medical School, Chicago, 1917; died in Rochester, Minn., Nov. 30, aged 70.

Greer, Dion Attus, Pikeville, Tenn.; University of the South Medical Department, Sewanee, Tenn., 1894; veteran of World War I; associated with the Bledsoe Memorial Hospital; member of the board of directors of the First National Bank; died in the Erlanger Hospital, Chattanooga, Dec. 7, aged 90.

Greusel, Charles Nicholas, San Diego, Calif.; Creighton University School of Medicine, Omaha, 1910; veteran of World War I; formerly staff member of St. Bernardine's Hospital in San Bernardino; died Oct. 31, aged 80.

Hallberg, John William Ⓜ Everton, Mo.; Northwestern University Medical School, Chicago, 1912; for many years on the staff of St. Luke's Hospital in Kansas City; died Nov. 12, aged 73.

Hamilton, Robert Stanford Ⓜ Port Angeles, Wash.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1924; member of the American Academy of General Practice; past-president of the Clallam County Medical Society; died in Montreal, Que., Canada, Nov. 11, aged 63.

Hanson, Lawrence Benton Ⓜ Santa Barbara, Calif.; State University of Iowa College of Medicine, Iowa City, 1929; served in the regular Army; veteran of World War II; died Dec. 2, aged 55.

Harquail, Raymond James, Greystone Park, N. J.; University of Montreal Faculty of Medicine, Montreal, Que., Canada, 1924; assistant clinical director of the New Jersey State Hospital; died in the All Souls Hospital, Morristown, Nov. 1, aged 63.

Harris, John Huggins, Houston, Texas; University of Texas School of Medicine, Galveston, 1923; member of the American Academy of Dermatology and Syphilology; specialist certified by the American Board of Dermatology; served on the faculty of the New York Medical College, Flower and Fifth Avenue Hospitals in New York City; veteran of World War I; formerly on the staff of the Manhattan State and Metropolitan hospitals in New York City; died Nov. 11, aged 62.

Healy, Cornelius Edward, Cincinnati; University of Illinois College of Medicine, Chicago, 1928; died Nov. 12, aged 60.

Herrick, Frank Leslie Ⓜ Livermore, Calif.; Oakland College of Medicine and Surgery, 1912; served as president of the Chamber of Commerce; high school football team physician for many years; died Nov. 12, aged 71.

Hunter, George Golden, Ironton, Ohio; Ohio State University College of Medicine, Columbus, 1917; a member of the Lawrence County Board of Education and the Ironton Board of Education; veteran of World Wars I and II; served in the Ohio House of Representatives and the Ohio Senate; served on the board of trustees of Ohio University; on the staff of the Lawrence County General Hospital, where he died Nov. 11, aged 71.

Hutchins, Amos Francis Ⓜ Arnold, Md.; born in Barstow, Sept. 29, 1884; Johns Hopkins University School of Medicine, Baltimore, 1913; member of the American Urological Association; fellow of the International College of Surgeons and the American College of Surgeons; veteran of World War I; served on the Anne Arundel County Board of Education; formerly on the faculty of his alma mater; associated with Anne Arundel General Hospital in Annapolis, the Church Home and Hospital, Bon Secours Hospital, and the West Baltimore General Hospital, in Baltimore; served on the board of governors of St. John's College in Annapolis; died in Baltimore Nov. 11, aged 75.

Hutchins, William Jackson Ⓜ Buford, Ga.; Atlanta College of Physicians and Surgeons, 1910; instrumental in the establishment of the Hutchins Memorial Hospital; died Nov. 12, aged 72.

Hyde, Harry C. Ⓜ Baltimore; University of Maryland School of Medicine, Baltimore, 1899; served on the faculty of his alma mater; at one time coroner; died in the Maryland General Hospital Nov. 19, aged 90.

Jordan, Sarah Murray, Marblehead Neck, Mass.; born in Newton Oct. 20, 1884; received a Ph.D. from the University of Munich in Germany in 1908; Tufts College Medical School, Boston, 1921; at one time taught at the Adelphi College in Brooklyn; specialist certified by the American Board of Internal Medicine; secretary, Section on Gastroenterology and Proctology, American Medical Association, from 1941 to 1946 and in 1947-1948 served as chairman; member and past-president of the American Gastroenterology Association; member of the Phi Beta Kappa and the Phi Beta Kappa Associates; fellow of the American College of Physicians; in 1952 received the Julius Friedenwald Medal; awarded the Elizabeth Blackwell Citation; in 1958 the Rockford (Ill.) College awarded her the Jane Addams Medal; for many years director of the gastroenterology department at the Lahey Clinic; in 1954 the fourth floor of the Frank H. Lahey Pavilion of the New England Baptist Hospital, Boston, was named in her honor; on the staff of the New England Deaconess Hospital in Boston; director of the Greater Boston Chamber of Commerce and was named vice-president of that organganization; awarded honorary degrees by Smith College, Tufts College, Wilson College, Suffolk University, and the Woman's Medical College of Pennsylvania in Philadelphia; a life trustee of Tufts College and a trustee of the Boston Museum of Science; served as chairman of the editorial board of *Gastroenterology;* conducted a medical column for two Boston newspapers; died in the New England Baptist Hospital, Boston, Nov. 21, aged 75.

Kennedy, Robert Otis Ⓜ Rushville, Ind.; Indiana University School of Medicine, Indianapolis, 1913; for many years county coroner; city and county health officer; on the retired staff of the Rush Memorial Hospital, where he died Nov. 7, aged 80.

Kenner, Albert Walton Ⓜ Major General, U. S. Army, retired, Washington, D. C.; George Washington University School of Medicine, Washington, D. C., 1915; Army Medical School, Washington, D. C., 1917; veteran of World Wars I and II; awarded the Distinguished Service Cross, Distinguished Service Medal with oak leaf cluster, the Silver Star and the Legion of Merit; from 1920 to 1922 instructor at the United States Military Academy; retired June 30, 1949; fellow of the American College of Surgeons; for many years associated with the Columbia Hospital for Women, where he died Nov. 12, aged 69.

Kern, Margaret Alexandra, Rock Creek, Ohio; University of Wooster Medical Department, Cleveland, 1902; for many years practiced in Conneaut; died Nov. 14, aged 89.

Lamb, Albert Richard Sr. Ⓜ Pine Orchard, Conn.; born in Waterbury April 22, 1881; Columbia University College of Physicians and Surgeons, New York City, 1907; fellow of the American College of Physicians; professor emeritus of clinical medicine at his alma mater, where he joined the faculty in 1913 and subsequently became professor of clinical medicine; veteran of World War I and attached to American Commission to Negotiate Peace; recipient of the Distinguished Service Medal from Columbia-Presbyterian Medical Center in New York City; consultant in medicine, physician, and honorary member of the medical board at the Presbyterian Hospital, New York City, serving as president of its medical board from 1940 to 1946; consulting physician at the Englewood (N. J.) Hospital; for many years associated with the Doctors Hospital in New York City; died Nov. 22, aged 78.

Leonard, Thomas Benjamin, Richmond, Va.; University College of Medicine, Richmond, 1904; also a pharmacist; veteran of World War I; served on the faculty of the Medical College of Virginia; died Nov. 11, aged 77.

Linton, Frank Terry Ⓜ Princeton, Ky.; University of Cincinnati College of Medicine, 1920; past-president of the Southwestern Kentucky Medical Association; died Nov. 2, aged 66.

Luongo, Gene Ignatius Ⓜ North Bergen, N. J.; Universita degli Studi di Bologna Facolta di Medicina e Chirurgia, Italy, 1952; veteran of World War II; interned at the Jersey City Hospital in Jersey City; died Nov. 16, aged 45.

McIntosh, Jesse Harrison Ⓜ Arcadia, Mo.; Barnes Medical College, St. Louis, 1895; veteran of World War I; served on the staff of the Alton (Ill.) State Hospital; died in the Veterans Administration Hospital, St. Louis, Nov. 10, aged 87.

McWilliams, Wiley Everett, Lexington, Ky.; University of Louisville Medical Department, 1911; veteran of World War I; died in the Veterans Administration Hospital Nov. 11, aged 78.

Morgan, Grady Alexander Ⓜ Asheville, N. C.; University of Tennessee College of Medicine, Memphis, 1917; veteran of World War I; served on the county board of health and as county health officer; associated with St. Joseph's, Aston Park, and Memorial Mission hospitals; died Oct. 29, aged 68.

Moursund, Walter Henrik Jr. Ⓜ Colonel, U. S. Army, Washington, D. C.; Baylor University College of Medicine, Dallas, Texas, 1934; served on the faculty of his alma mater; specialist certified by the American Board of Internal Medicine; entered the military service in 1940; served during World War II and later in Korea; held the Legion of Merit; formerly on the staff of the Parkland Hospital in Dallas; chief of Army Physical Standards; died in the Walter Reed Army Hospital Nov. 20, aged 50.

Munn, Alfred Alexander Ⓜ Chicago; Chicago Medical School, 1934; intern, Holy Cross Hospital in Salt Lake City, Utah; served as a captain in the U. S. Army during World War II; died in the Veterans Administration Center, Los Angeles, Nov. 4, aged 59.

Nelson, Melvin Sylvanus Ⓜ Granite Falls, Minn.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1908; formerly associated with the Indian Service; past-vice-president of the Minnesota State Medical Association; died in the Granite Falls Hospital Nov. 10, aged 77.

Nichols, Clay Lloyd Ⓜ Louisville, Ky.; Louisville Medical College, 1903; veteran of World War I; formerly taught at his alma mater; on the staffs of the Norton Memorial Infirmary, Jewish Hospital, and SS Mary and Elizabeth Hospital; for many years district surgeon for the Illinois Central Railroad; died Nov. 10, aged 77.

Paye, Philip Horace Ⓜ Cadillac, Mich.; St. Louis University School of Medicine, 1936; member of the Radiological Society of North America; at one time associated with the U. S. Public Health Service in Washington, D. C.; veteran of World War II; on the staff of the Mercy Hospital, where he died Nov. 6, aged 50.

Pearce, Elizabeth Katherine Youngman, Wichita, Kan.; University of Oklahoma School of Medicine, Oklahoma City, 1911; died in the Wesley Hospital Nov. 8, aged 82.

Perelson, Harold Nathan Ⓜ Inglewood, Calif.; Long Island College of Medicine, Brooklyn, 1935; specialist certified by the American Board of Internal Medicine; member of the American College of Cardiology; served on the faculty of the University of Southern California School of Medicine in Los Angeles; died Dec. 5, aged 50.

Perkins, Clifton Todd Ⓜ Towson, Md.; Boston University School of Medicine, 1926; certified by the National Board of Medical Examiners; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; formerly on the faculty of his alma mater; since 1950 commissioner of mental hygiene for Maryland; for 12 years commissioner of mental hygiene for Massachusetts; at one time on the staff of the Worcester (Mass.) State Hospital; died Nov. 10, aged 58.

Pollok, Lewis William Ⓜ Temple, Texas; University of Virginia School of Medicine, Charlottesville, 1902; fellow of the American College of Surgeons; associated with King's Daughters Hospital, where he died Nov. 21, aged 79.

Powers, Harris Earle Ⓜ Manchester, N. H.; Tufts College Medical School, Boston, 1916; fellow of the American College of Surgeons; served on the staffs of the Elliott, Notre Dame de Lourdes, and Sacred Heart hospitals; died Nov. 4, aged 67.

Reichard, Orill Ⓜ Flint, Mich.; University and Bellevue Hospital Medical College, New York City, 1905; associated with the McLaren and St. Joseph hospitals, and the Hurley Hospital, where he died Nov. 10, aged 81.

Reichman, John Joseph, Hannibal, Mo.; St. Louis University School of Medicine, 1929; on the staffs of the Levering and St. Elizabeth hospitals; died Nov. 6, aged 53.

Romonek, Philip L. Ⓜ Beverly Hills, Calif.; Loyola University School of Medicine, Chicago, 1921; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; on the faculty of the University of California at Los Angeles School of Medicine; at one time on the faculty of the University of Nebraska College of Medicine in Omaha, where he was on the staff of the Lutheran Hospital; served on the staffs of St. John's Hospital in Santa Monica and Cedars of Lebanon Hospital in Los Angeles; died in the Mount Sinai Hospital in Los Angeles, Nov. 9, aged 64.

Rudderow, Edward Douglas Ⓜ New York City; New York Homeopathic Medical College and Hospital, New York City, 1895; served on the faculty of the New York Medical College and Hospital for Women and his *alma mater*; veteran of World War I; on the welfare board of the Metropolitan Hospital; on the staff of the Flower and Fifth Avenue hospitals; died in Stamford, Conn., Nov. 15, aged 87.

Rusmisell, James Adam Ⓜ Buckhannon, W. Va.; Maryland Medical College, Baltimore, 1904; veteran of World War I; on the staff of the Elizabeth Coplin Leonard Hospital, where he died Nov. 4, aged 80.

Rutherford, Samuel C. Ⓜ Tulsa, Okla.; University of Arkansas School of Medicine, Little Rock, 1901; died in Pryor Nov. 13, aged 90.

Santo, Ralph Verrei, Abington, Pa.; Temple University School of Medicine, Philadelphia, 1945; interned at the Newark City Hospital and St. James Hospital in Newark, N. J.; veteran of World War II; died Nov. 5, aged 40.

Saphir, Joseph Frederick Ⓜ Peekskill, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1902; member of the American Proctologic Society; served as an honorary surgeon of the New York City Police Department; formerly chief of proctology at Manhattan State Hospital, New York City; died Nov. 26, aged 78.

Saxe, Le Roy Hallowell, Shippensburg, Pa.; Jefferson Medical College of Philadelphia, 1905; past-president of the Franklin County Medical Society; served on the staff of the Carlisle (Pa.) Hospital; died Oct. 21, aged 80.

Schaiberger, Elmer George Ⓜ Birch Run, Mich.; University of Michigan Medical School, Ann Arbor, 1928; interned at St. Mary's Hospital in Grand Rapids; formerly practiced in Saginaw, where he was county coroner; died in St. Joseph's Retreat Hospital, Dearborn, Oct. 30, aged 59.

Schott, Theodore Joseph Ⓜ Yakima, Wash.; St. Louis University School of Medicine, 1928; on the staff of St. Elizabeth Hospital; died in the University Hospital, Seattle, Oct. 31, aged 55.

Schwartz, Frederick Leonhardt Ⓜ San Diego, Calif.; University of Buffalo School of Medicine, 1917; fellow of the American College of Surgeons and the International College of Surgeons; formerly served in the regular U. S. Navy; associated with the Mercy Hospital; on the staff of the Scripps Memorial Hospital in La Jolla; died Nov. 13, aged 62.

Schwarz, Rudolph Ⓜ Phoenix, Ariz.; Medizinische Fakultät der Universität, Vienna, Austria, 1921; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; served as senior clinical psychiatrist at Sing Sing Prison; died Nov. 1, aged 64.

Sealover, William Frederic, Zanesville, Ohio; Starling Medical College, Columbus, 1900; veteran of World War I; on the staffs of the Bethesda and Good Samaritan hospitals; died Nov. 9, aged 81.

Sennott, John Ralph Ⓜ Cambridge, Mass.; Harvard Medical School, Boston, 1902; served on the staffs of the Cambridge City Hospital and the Holy Ghost Hospital; died Nov. 17, aged 81.

Smith, John Wesley, Gassaway, W. Va.; University of the South Medical Department, Sewanee, Tenn., 1898; died Nov. 10, aged 86.

Soanes, Jabez George N. Ⓜ Kansas City, Kan.; Howard University College of Medicine, Washington, D. C., 1901; for many years police surgeon; died in the Douglass Hospital Nov. 5, aged 85.

Spector, Isaac, St. Louis; Baltimore Medical College, 1905; died in the Jewish Hospital Oct. 17, aged 86.

Stapleton, Willard Pierce, Gardner, Mass.; Bennett Medical College, Chicago, 1915; veteran of World War I; served on the staff of the Henry Heywood Memorial Hospital; died Nov. 4, aged 67.

Stickney, Whitman Gibson, Beverly, Mass.; Tufts College Medical School, Boston, 1901; for many years medical examiner in the Seventh Essex District; served as school physician; died Nov. 17, aged 90.

Stowell, Fred Austin Ⓜ Newburyport, Mass.; Pulte Medical College, Homeopathic, Cincinnati, 1902; died Oct. 26, aged 92.

Swallum, James Alva, Storm Lake, Iowa; the Hahnemann Medical College and Hospital, Chicago, 1901; died in the Sioux Valley Hospital, Cherokee, Sept. 11, aged 85.

Swan, Alfred Hjalmar Ⓜ Pearblossom, Calif.; Rush Medical College, Chicago, 1921; for many years practiced in Shanghai, China; died Nov. 3, aged 75.

Swanson, John Theodore Ⓜ Independence, Kan.; University of Kansas School of Medicine, Kansas City, 1908; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; veteran of World War I; served on the staff of the Mercy Hospital; died Nov. 16, aged 80.

Tabor, Sidney Johnston Ⓜ Portsmouth, Va.; Vanderbilt University College of Medicine, Nashville, Tenn., 1892; died Nov. 9, aged 92.

Taylor, Zella Eileen, Winchester, Mass.; Boston University School of Medicine, 1933; interned at the Mary Hitchcock Memorial Hospital in Hanover, N. H., and the Hospital for Women, Baltimore; certified by the National Board of Medical Examiners; died Nov. 1, aged 53.

Thomas, Charles Anslem Ⓜ Tucson, Ariz.; Medical Department of Tulane University of Louisiana, New Orleans, 1905; formerly associated with the Indian Service; fellow of the American College of Surgeons; past-president of the Southwestern Medical Association, Pima County Medical Society, and the Arizona Medical Association; veteran of World War I; past-president and honorary member of the staff of St. Mary's Hospital and was a member of the staff of the Tucson Medical Center; died Nov. 5, aged 82.

Tolleson, George W., Amity, Ark.; University of Arkansas School of Medicine, Little Rock, 1898; one of the founders of the Pike County Bank, Murfreesboro; president of the Bank of Amity; died in Hope Nov. 12, aged 89.

Townsend, Willis Merrick Ⓜ Melrose, Mass.; Boston University School of Medicine, 1893; for many years associated with the Melrose Hospital; died Nov. 11, aged 89.

Trescher, John Henry Ⓜ Baltimore; Cornell University Medical College, New York City, 1924; member of the American Academy of Allergy; associated with the Johns Hopkins Hospital, Union Memorial Hospital, Hospital for the Women of Maryland, and Sinai Hospital; died Nov. 15, aged 60.

Trimble, Volantus G., Somerset, Ky.; University of Louisville Medical Department, 1909; veteran of the Spanish-American War; died in the Somerset City Hospital Oct. 9, aged 82.

Turner, Vernon C. Ⓜ Evanston, Ill.; born in Banks, Ore., Sept. 19, 1907; University of Oregon Medical School, Portland, 1936; specialist certified by the American Board of Orthopaedic Surgery; member of the Clinical Orthopaedic Society, American Academy of Orthopaedic Surgery, and of the American Rheumatism Association; fellow of the International College of Surgeons and the American College of Surgeons; past-president of the Chicago Orthopaedic Society; member of the medical advisory committee of the Arthritis Foundation; served as associate professor of orthopaedic surgery, Northwestern University Medical School; for many years on the staff of the Evanston Hospital; consultant, Swedish Covenant Hospital; died Nov. 21, aged 52.

Tylbor, Rubin, New York City; Uniwersytet Jozefa Pilsudskiego, Warszawa, Poland, 1926; served a residency at the Willard Parker Hospital; died Nov. 8, aged 63.

Vance, James Ⓜ El Paso, Texas; Hospital College of Medicine, Louisville, Ky., 1899; past-president of the El Paso County Medical Association and the Southwestern Medical and Surgical Association; while in Louisville, Ky., served as president of the Louisville Surgical Society; served on the faculty of the University of Louisville (Ky.) School of Medicine; veteran of World War I; fellow of the American College of Surgeons; associated with Hotel Dieu, Sisters Hospital, Southwestern General and Providence Memorial hospitals; died Dec. 2, aged 84.

Van Voorhis, Clyde Randolph, Prairie City, Iowa; Drake University College of Medicine, Des Moines, 1904; veteran of World War I; for many years on the staff of the Iowa Lutheran Hospital in Des Moines; died in the Veterans Administration Hospital, Des Moines, Nov. 10, aged 82.

Vian, George Martin Vaznaian Ⓜ Woonsocket, R. I.; Georgetown University School of Medicine, Washington, D. C., 1939; veteran of World War II; served on the staffs of St. Joseph's Hospital in Providence, and Woonsocket Hospital; died Nov. 8, aged 45.

Walsh, Arthur F. Ⓜ Grafton, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1899; died in the Mercy Hospital, Pittsburgh, Nov. 3, aged 84.

Waugh, Richey Laughlin Ⓜ Medical Director, U. S. Public Health Service, retired, Arlington, Mass.; University of Minnesota Medical School, Minneapolis, 1915; member of the American Academy of

Orthopaedic Surgeons and the American Association for the Surgery of Trauma; fellow of the American College of Surgeons; in 1947 awarded the Founders Medal of the Association of Military Surgeons of the United States; died Nov. 24, aged 71.

Webster, Daniel Jefferson Ⓜ Ironton, Ohio; Miami Medical College, Cincinnati, 1893; past-president of the Lawrence County Medical Society; died Nov. 21, aged 92.

Weil, Frederic Samuel Ⓜ New York City; Universität Basel Medizinische Fakultät, Switzerland, 1927; specialist certified by the American Board of Psychiatry and Neurology; member of the American Academy of Neurology and the American Psychiatric Association; faculty member of the New York Psychoanalytic Institute; from 1942 to 1947 adjunct psychiatrist at Mount Sinai Hospital; died in the Doctors Hospital Nov. 6, aged 59.

West, Edward McMichael Ⓜ Atlanta, Ga.; Medical College of Georgia, Augusta, 1946; on the staff of the Grady Hospital; died Nov. 13, aged 38.

Wharton, May Cravath Ⓜ Pleasant Hill, Tenn.; University of Michigan Homeopathic Medical School, Ann Arbor, 1903; founded the Uplands Cumberland Sanatorium; died Nov. 19, aged 86.

White, Hal Hugh Ⓜ Paris, Texas; University of Louisville (Ky.) Medical Department, 1901; fellow of the American College of Surgeons; associated with the Sanitorium of Paris, where he died Nov. 21, aged 82.

Whitmer, Ralph Glenn Ⓜ Des Moines, Iowa; Rush Medical College, Chicago, 1927; member of the American Academy of General Practice; veteran of World Wars I and II; formerly on the staffs of the West Suburban Hospital in Oak Park, Ill., and the Community General Hospital in Sterling, Ill.; associated with the Veterans Administration Hospital; died Nov. 12, aged 70.

Wiesbader, Hans Wilhelm Ⓜ New York City; Universität Heidelberg Medizinische Fakultät, Baden, Germany, 1923; on the staff of the Bellevue Hospital; died in the Montefiore Hospital Nov. 4, aged 59.

Williams, Arthur Frederick Ⓜ Fort Morgan, Colo.; Denver and Gross College of Medicine, 1903; member of the Radiological Society of North America; died Nov. 21, aged 78.

Williams, Earle Ⓜ Brooklyn, Ill.; Jenner Medical College, Chicago, 1907; member of the American Academy of General Practice; past-president of the board of education; member of the staffs of St. Mary's and Christian Welfare hospitals in East St. Louis, St. Elizabeth's Hospital of Granite City, St. Mary's Infirmary and People's Hospital in St. Louis; died Nov. 5, aged 74.

Williams, Hiram Griffith Ⓜ Prentiss, Miss.; Atlanta College of Physicians and Surgeons, 1902; died in the Jefferson Davis County Hospital Nov. 12, aged 84.

Williams, Robert Vincent Ⓜ Flushing, N. Y.; Fordham University School of Medicine, 1913; veteran of World War I; for many years police surgeon; associated with the Midtown Hospital, New York City, and Flushing Hospital, where he was past-president of the medical board and where he died Nov. 18, aged 73.

Willis, Jack Edward Ⓜ Mill Valley, Calif.; Stanford University School of Medicine, San Francisco, 1945; interned at the Stanford University Hospitals, San Francisco, where he served a residency; formerly a resident at the San Francisco Hospital; resigned from the regular U. S. Army June 17, 1952; associated with the Marin General and San Rafael General hospitals; died in the California Medical Facility, Department of Corrections, Vacaville, Nov. 24, aged 41.

Wiseley, Allen Newton, South Laguna, Calif.; Rush Medical College, Chicago, 1913; formerly practiced in Lima, Ohio, where he was past-president of the Allen County Academy of Medicine, and member of the city board of education; served on the staff of the Lima Memorial and St. Rita's hospitals in Lima, Ohio; died Nov. 2, aged 76.

Workman, Meyer, New York City; University and Bellevue Hospital Medical College, New York City, 1918; died in the New York Hospital Oct. 29, aged 63.

Wood, Gordon Lee Ⓜ Andalusia, Ala.; University of Alabama School of Medicine, Mobile, 1910; affiliated with the Covington Memorial Hospital; died in St. Margaret's Hospital, Montgomery, Oct. 28, aged 76.

Worthington, Arthur Morton Ⓜ Dedham, Mass.; Harvard Medical School, Boston, 1896; served on the faculty of his alma mater; for many years bacteriologist for the board of health; past-president of the Dedham Historical Society; veteran of World War I; died Nov. 11, aged 89.

Wright, James J. C., Rockmart, Ga.; Hospital Medical College, Eclectic, Atlanta, 1909; died Oct. 27, aged 72.

Wyser, Dorean David, Ossining, N. Y.; Medizinische Fakultät der Universität, Wien, Austria, 1920; specialist certified by the American Board of Radiology; member of the American College of Radiology; served on the staffs of the Peekskill (N. Y.) Hospital and the Ossining Hospital; died Nov. 6, aged 67.

FOREIGN LETTERS

GERMANY

Problems of Blood Transfusion.—W. Lutzeyer (*Arch. klin. Chir.* 290:576, 1959) stated that the number of blood transfusions given has increased tenfold in the last 10 years. Although cross-matching should be done on every patient, subtyping of group A can be ignored since the purpose of cross-matching is to discover irregular cold antibodies. From a serologic point of view there are no donors whose blood can be used for any patient. The group O donor possesses a high titer of agglutinins and isohemolysins in 4 or 5% of cases. The use of group O, Rh negative, blood is justified only under unusual circumstances. A questionnaire sent to 80 blood banks revealed that cross-matching was usually performed in only one direction. Of those blood banks 66 denied that there was an increased incidence of transfusion reactions in patients with group A blood.

To avoid pyrogenic reactions stored blood should not be given before the 3rd day or later than the 14th day after donation. A definite decrease in the incidence of reactions to transfusions since the introduction of stored blood was reported by 72 banks. The incidence of pyrogenic reactions to stored blood was 0.3 to 2.5%. A further significant reduction in the incidence of these reactions followed the introduction of the disposable transfusion kits. The addition of drugs to stored blood to prevent pyrogenic reactions was not recommended. About 4% of stored blood was bacterially contaminated, chiefly with coliform organisms. Sterility tests increase the danger of bacterial contamination. According to the replies 56 of the banks had seen no bacteriotoxic reactions to transfusion. Stored blood which is no longer vacuum-sealed, or which has undergone obvious hemolysis, should always be suspected of contamination. The addition of 0.2 Gm. of leukomycin to each bottle reduced the incidence of reactions by a further 33% without causing allergic symptoms. The most frequent cause of accidents was air embolism resulting from transfusion under pressure.

Transfusion with fresh blood may cause a delay in clotting. Stored blood coagulates best about five days after it has been taken. In patients with acquired or congenital anomalies of coagulation (e. g., hemophilia), however, the tendency to increase bleeding is aggravated by transfusion with stored blood. The tendency of some surgical patients to excessive bleeding may be due to (1) faulty transfusion technique, masked by the anesthetic, (2) pyrogenic reactions, (3) extensive operations on the lung, (4) fall in blood pressure during operation, (5) hypothermia, or (6) preoperatively given anticoagulants or antibiotics.

Mucoviscidosis.—E. Koch of Giessen (*Deutsche med. Wchnschr.* 84:1773, 1959) stated that hereditary mucoviscidosis occurs even more frequently in adults than in infants and children. The cause of the condition is a disturbance of the function of many of the exocrine glands, which take the form of the secretion of an abnormally viscid mucus. The diagnosis is based on excretory pancreatic insufficiency (due to cystic fibrosis of the pancreas), bronchiectasis, pulmonary emphysema, and a constantly raised level of sodium and chloride in the sweat combined with mineral loss and low blood pressure. Investigation of 41 families in which mucoviscidosis was found showed the condition to be inherited as an autosomal dominant gene.

Of 41 adults with hereditary mucoviscidosis 17 were found to have florid or healed peptic ulcers. In 12 of the families investigated 19 relatives were also found to have peptic ulcer and mucoviscidosis. A high incidence of peptic ulcers was found in the families of patients in this series who had no evidence of ulcer. Two patients died as a result of the pulmonary emphysema and cor pulmonale. Postmortem examination confirmed the clinically recognized combination of mucoviscidosis and duodenal ulcer. This is the first time that mucoviscidosis has been recognized clinically and pathologically in an adult. Of 43 selected ulcer patients all the cardinal symptoms of mucoviscidosis were well developed in 4, and many others showed one or more of these symptoms. Raised electrolyte concentrations in the sweat were found in 9, early pulmonary emphysema in 9, and a marked reduction or absence of one or more of the pancreatic enzymes in the duodenal juice in 25. Half of the patients with peptic ulcer showed none of the cardinal symptoms of mucoviscidosis.

In order to test the specificity of the cardinal symptoms 35 patients with cholangitis or hepatitis and a varying degree of pancreatic involvement were investigated. Of these, 12 showed a uniform and marked decrease in all the enzymes of the duodenal juice, i. e., not the dissociated decrease characteristic of mucoviscidosis. Electrolytic disturbances, on the other hand, were always absent. In-

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The items in these letters are contributed by regular correspondents in the various foreign countries.

vestigation of 32 healthy subjects and 88 patients with various conditions showed normal electrolyte concentrations in the sweat and normal pancreatic enzyme activity.

The incidence of peptic ulcer and mucoviscidosis in combination was at least 10 times as common as it would be in a random distribution. This was probably due to the structural changes in the gastric and duodenal mucosa. According to the pathologists the histological changes in the gastrointestinal mucosa in mucoviscidosis are as great as those in the pancreas and the bronchial tree. Apart from these inherent anomalies, trauma or irritation play a role. The fact that certain families show an increased incidence of peptic ulcers is adequately explained by these findings.

Treatment of Psychoses.—Dickhaut and Pyrkosch of Hamburg (*Nervenarzt* 29:367-370, 1958) said that successful results of treatment with promazine were reported in 850 patients with acute psychoses. In 85% of the patients the symptoms were controlled immediately. In one of the closed wards of the Hamburg psychiatric clinic a further 85 patients were treated with promazine. Over a total period of three months 100 to 200 mg. of promazine was given three or four times daily to each patient for 2 to 32 days at a time. The patients treated in this way had alcoholic delirium, postrheumatic psychoses, arteriosclerotic agitation, and endogenous psychoses. Promazine was as effective as chlorpromazine. The toxicity of promazine was less but the duration of its effect was shorter. Like chlorpromazine it had a purely symptomatic effect. No undesirable side-effects were observed. Intravenous injection produced an immediate tranquilizing effect. Intravenously given doses of hypnotics, analgesics, and narcotics had a stronger effect than oral doses. Promazine is a serviceable drug which acts at a subcortical level to depress psychomotor excitement of various origins.

Antibiotic-Resistant Staphylococci.—H. G. Fischer (*Deutsche med. Wchnschr.* 84:257-258, 1959) said that not all hemolytic staphylococci are resistant to antibiotics. The following resistances were found for staphylococci: 57% were resistant to penicillin, 45% to streptomycin, 13% to tetracycline, and 2% to chloramphenicol. One must, however, take into account the source of the material sent in for culture. For instance, 57% of all strains isolated in the Kiel University clinic were resistant to penicillin, whereas in general practice only 25% were thus resistant. In the surgical outpatient department of the university the rate went as high as 73%. If it be remembered, too, that practitioners usually take cultures for sensitivity tests only if treatment with an antibiotic has failed, then it must be assumed that the true resistance rate is even lower than 25%.

Iron and Copper Metabolism and Malignancy.—E. Kautzsch (*Medizinische* no. 40, p. 1851, 1959) stated that malignant neoplasms are associated with a characteristic alteration in serum iron and serum copper levels. Epithelial and mesenchymal new growths behave similarly with a moderate reduction in the level of the transport iron and an increase in the level of serum copper. The findings are similar to those in persons with acute and chronic infections (type 2). Hemorrhage associated with neoplastic disease gives rise to a particularly severe fall in the serum iron level (a combination of functional types 2 and 4). Neoplasms of the hemopoietic system (leukemia, multiple myeloma, lymphogranulomatosis, etc.) behave in principle similarly to other neoplasms except that increased hemolysis coupled with a decreased rate of erythropoiesis tends to have a dominant effect on the clearance of iron from the serum. In such cases raised serum copper levels are found in combination with markedly raised levels of serum transport iron (a combination of functional types 2 and 3).

It appears from investigations of 200 patients that no particular degree of alteration in the level of the serum transport iron can be ascribed to any particular type or site of neoplasia. In contrast, markedly raised serum copper levels (over 200 mcg. per 100 ml.) always suggest prostatic carcinoma or Hodgkin's disease. In the treatment of neoplastic disease by cytostatic drugs or surgery the serum iron and copper levels are a valuable guide to the success of the treatment and an indication of metastasis formation.

Dishabituation to Nicotine.—Jost and Jochum (*Med. Klin.* 54:1049, 1959) said that nicotine is contraindicated in patients with myocardial insufficiency, coronary thrombosis, thromboangiitis obliterans, arteriosclerotic disturbances of circulation, and angina pectoris. The so-called nicotine-free tobaccos still contain 0.1 to 0.2% of nicotine. Filter tips generally eliminate the noncarcinogenic hydrophilic substances but not the fat-soluble carcinogenic substances and nicotine. Thus the only way to avoid nicotine is to give up smoking.

Rinsing the mouth with silver nitrate, sucking tablets, or chewing gum to spoil the taste of cigarettes, and using various ethereal oils and quinine compounds has, for the most part, failed to have any lasting effect. Patients have, however, been enabled to give up smoking after treatment with lobeline, which has an antagonistic effect on nicotine. The patients are given 10 mg. of lobeline in a glass of water, and this is drunk a mouthful at a time throughout the day. Treatment lasts 10 to 14 days. Even better results are achieved with resident patients in a "dishabituation collective" where psychotherapy can also be used. In such circumstances patients are given 20 mg. of lobeline intramuscularly one to three times a day. Generally the first symptoms are apparent within 12 to 24 hours. They take the form of nausea, vomiting, fall in skin temperature, fall in blood pressure, sweating, giddiness, headache, and loss of taste for cigarettes. This symptom-complex occurs only when a cigarette is smoked and seldom gives rise to collapse. If the treatment is not successful within 14 days the patient should be given a rest, since the effects can be produced again only after an interval if no positive results have been obtained in the first instance.

Renal Tumors in Childhood.—P. Kolle of Munich (*Deutsche med. Wchnschr.* 84:1256-1260, 1959) stated that in 1930 tumors were not among the 10 commonest causes of death in childhood. Today, however, they are the second commonest cause. Foremost among such tumors are the embryonal mixed renal tumors, or Wilms's tumors, which comprise 20% of all tumors of childhood. These embryonal tumors also occur in adults and may grow to an extraordinary size. In half the patients metastases are already demonstrable by the time the diagnosis is made, and these are generally situated in lung and liver as well as in the regional and para-aortic lymph nodes. Diagnosis is difficult, since the tumor itself is often the only symptom. Hematuria occurs in only 10 to 20% of cases and bears an unfavorable prognosis. Signs of ileus and generalized systemic symptoms indicate the presence of metastases. In the differential diagnosis neuroblastoma, hydronephrosis, and retroperitoneal sarcoma must be ruled out. The diagnosis can be confirmed by gentle palpation and by pyelography. Renal biopsy is contraindicated because of the danger of dissemination.

The treatment of choice seems to be nephrectomy followed immediately by radiotherapy with 4,000 to 5,000 r and possibly preceded by irradiation to reduce the size of the tumor before operation. Recurrences occur generally within the first year so that the two-year cure rate is essentially equivalent to the five-year cure rate in adults. If the operation is performed as soon as possible the chances of cure are about 20%, and they increase with increasing age in childhood. The prognosis is most favorable if the diagnosis is made in the first half-year of life and treatment is begun at once.

Vesical Carcinoma.—Sievers and Marzoli of Kiel University (*Med. Klin.* 54:366-368, 1959) used DG 428 in the treatment of 27 patients who had carcinoma of the bladder. DG 428 is a synthetic thymine derivative and antimetabolite which interferes with glycolysis in the tumor cells, thus inhibiting their growth. Inhibition of tumor growth, confirmed by cystoscopy, was accompanied by a marked decrease in the severity of urinary symptoms and tenesmus. Blood and liver function were checked regularly as a safety measure. No leukopenic changes or liver damage were observed. Seven of the 27 patients died of uremia and metastases. Only 3 of the remaining 20 had bladder symptoms when they were last examined, and in these 3 the treatment had no effect on the growth of the tumor. Seventeen patients were symptom-free and were able to do part-time work. On the average they were able to go five hours without passing urine. The average capacity of the bladder was 80 cc. four weeks after the start of treatment and was 250 cc. in all patients when they were last seen. Eight patients have been observed for more than a year and two for more than two years. A marked regression of the tumor has been confirmed in 6 of the 17 patients by cystoscopy and radiography. In the others only an inhibition of the growth occurred.

Sulfobromophthalein Clearance.—Examination of 51 patients with proved chronic liver disease led A. Krautwald and co-workers of Berlin (*München. med. Wchnschr.* 101:2057, 1959) to conclude that the sulfobromophthalein clearance test is prolonged in patients with (1) chronic hepatitis, (2) chronic hepatitis passing into cirrhosis, or (3) cirrhosis. The extent of the prolongation paralleled the severity of the liver damage. Electrophoretically, the decrease in albumin levels and the increase in γ-globulin levels were significant only in the third group. While the second group showed a pronounced tendency toward the above-mentioned changes in albumin and γ-globulin levels, electrophoresis could not be used by itself diagnostically in the patients of group 1. Determination of prothrombin time did not show a definite lowering in any of the patients in this series. In the early stages of general liver damage the sulfobromphthalein test gave the most reliable results of all the procedures used.

HUNGARY

Bronchial Asthma.—K. Hajós and M. Hajós (*Acta allergol.* 14:87-99, 1959) reported that in a group of 1,000 asthmatic patients the environment influenced the course of the disease and therapeutic results. Family conflicts affected adversely 163 patients of the series, economic changes 241, and the intensification of psychic stress during the war 143. Apart from a number of asthmatic attacks evidently caused by occupation, the patient's profession per se was responsible for deterioration in 124 patients. Change of profession (physical to intellectual and vice versa) had no significant influence. The welfare of asthmatic persons did not depend entirely on organized therapy but on consecutive lesions and secondary diseases as well. Emphysema was seen in 748, chronic bronchitis in 392, and signs of right heart preponderance in 221 patients. Genuine asthmatic death occurred in 158. Therapeutic success, working capacity, and duration of the disease seemed to be influenced by preventable stresses.

INDIA

Family Planning.—That the idea of spacing childbirth is gaining support is evident from the increased number of persons who are attending family planning clinics (*Pharmaceutist*, vol. 5, Nov., 1959). On the average, over 14,550 people attend these clinics every month in the state of Uttar Pradesh. From Sept. 1, 1958, to Aug. 31, 1959, 2,123 persons were voluntarily sterilized at these clinics, which render free service to all. Of this number the women outnumbered the men six to one.

NORWAY

Comparison of Drugs for the Relief of Labor Pain.—The pain-relieving effect of 100 mg. of meperidine and 30 mg. of dihydrocodeine were compared in 419 women during labor by Lund and Lind (*Acta anaesth. scandinav.*, supp. 2, pp. 41-48, 1959). The analgesic effects of the drugs were rated as good when more than 50%, fair when 50%, and poor when less than 50% relief from pain was achieved. When the total number of doses for each drug were compared, meperidine gave good relief in 64.2% as compared to 41.4% when dihydrocodeine was used. The authors concluded that 100 mg. of meperidine was far from being an ideal analgesic in childbirth, although it is regarded as much safer than morphine. This belief has prevailed in spite of the fact that the respiratory depression caused by meperidine was as severe or more severe than that caused by equianalgesic doses of morphine. In spite of the strict indications for the use of analgesics in the present series, the newborn infants seemed to have been affected to some extent by the use of meperidine. No such effect could be demonstrated in the infants whose mothers had received dihydrocodeine.

UNITED KINGDOM

Call To Drop Patients' Fee.—A call to the government to abolish all charges to patients using the National Health Service was made by the councils which administer the family doctor, dental, pharmaceutical and ophthalmic services. In a memorandum to the Minister of Health, the Joint Committee of Associations of Executive Councils says the charges are preventing people from having necessary treatment. They are causing hardship, particularly to the older people and those with large families. When it was introduced in 1948 the Health Service was free of charge, with a few minor exceptions. Beginning in 1952, charges have been introduced for medicines and appliances, dental treatment, and glasses, but the comparatively small income derived from patients' charges is outweighed by the disadvantages inherent in the system, particularly the deterrent effect on persons requiring treatment. Estimated total gross Exchequer expenditure on the Health Service for the United Kingdom in the year ended on March 31 was 1,954 million dollars. Patients' payments were expected to amount to 80.6 million dollars or about 4%. Receipts from Health Service contributions, introduced in 1957, were put at 300 million dollars, or just over 15%.

Prophylactic Use of Isoniazid in Infants.—Infants are the most susceptible of all persons to tuberculous infection, and in countries with advanced medical and social care separation of newborn infants from tuberculous mothers is practiced whenever possible, and the infants are artificially fed. In primitive communities, however, the artificial feeding of infants is difficult and hazardous, and if they are not breast fed many of them die from gastroenteritis. Dormer and co-workers in Durbin, faced with the appalling mortality of African infants separated from their mothers, decided to treat with isoniazid all babies born in hospital of mothers with active tuberculosis (*Lancet* 2:902, 1959). The mothers were allowed to nurse their babies if they were well enough to do so. A series of 98 newborn infants were kept in cribs by their mothers, and from birth until the age of 6 months they were given 25 mg. of isoniazid in syrup daily. After six months the dosage was increased to 50 mg. twice daily. No adverse effects on the infants were noted. All but six of them were breast fed, and the mothers who were well enough helped with the care of their children. All the mothers had active pulmonary tuberculosis, and no special precautions were taken to prevent infection. Tuberculin tests were made monthly and roentgenograms of the chest every two months.

Seven of the children became tuberculin positive, but in four of them this was due to inadequate medication with isoniazid. Apart from two deaths there was no evidence of deterioration in the mothers after pregnancy or during lactation. The authors concluded that isoniazid given prophylactically to these newborn native children can almost completely protect them from tuberculosis, but infants so protected do not develop immunity and, as soon as the drug therapy is stopped, are likely to develop the disease. BCG vaccine was not given, as tuberculin conversion was the most important method of detecting infection. It is proposed in the future to give isoniazid-resistant BCG vaccine to all infants before they leave the hospital.

Antibiotics Help Life Insurance.—Many applicants for life insurance who have suffered from what were formerly grave, and often fatal, maladies can now be accepted after recovery, at first class rates, according to Dr. T. W. Preston. Pneumonia, meningitis, and various forms of septicemia are now readily brought under control. Osteomyelitis, in its chronic form, before the era of antibiotics, made the subject a poor insurance risk. These now respond to penicillin therapy immediately, in most cases. One of the most revolutionary changes is in the attitude toward venereal disease. A history of gonorrhea is now no bar to first class acceptance, and with satisfactory evidence of a cure and a negative blood test result, there is now no reason why the syphilitic patient should not be accepted at standard rates after two years. Records of a series of 3,277 cases of pulmonary tuberculosis accepted for insurance between 1947 and 1957 showed that only 7 persons died from tuberculosis and 19 from other causes. This gave a mortality well within the limits of expected rates. Patients who had suffered from tuberculosis of organs other than the lungs are usually acceptable for insurance after a few years. Similar considerations apply to several types of anemia. Experience has not, however, encouraged a more liberal outlook in the acceptance of patients with peptic ulcer. Those with heart disease and cancer are still not insurable.

The Hospital Service.—In a debate on the hospital service of Britain in the House of Lords, Lord Stonham attacked the Treasury and the bureaucracy of the Ministry of Health. He said that the achievements of the ordinary regional hospitals had been made against a disgraceful background of exploitation and parsimony. Less money is being spent on health now than before the war. It has been possible to spend less and do more work only by relying on the traditions, goodwill, devotion, and, indeed, the sweated labor of those who work in the National Health Service. The country is therefore still enjoying a first-class service on second-class payment. The goodwill that enables it to do this is fast running out. Lord Stonham said that only 3.5% of the total expenditure went for maintenance. This resulted in low standards of cleanliness in many hospitals, particularly in London. It is ludicrous for the Ministry to send out directives on the prevention of hospital cross-infection if it cannot keep the hospitals clean. Lord Stonham also asked for a fair deal for ancillary and nonmedical staffs.

Viscount Waverley, a physician at the Royal Berkshire Hospital, said that the outpatient clinics, special departments, and wards were overcrowded. The turnover of patients had been speeded up so much that there was a risk of staff breakdown from fatigue and of inadequate investigation and treatment. Another result was a shortage of nurses, physiotherapists, radiographers, and technicians. Valuable original work was not fostered by the present conditions in the health service. The hospitals deserved greater support. A massive program of new hospital construction was needed. The present prospects were disappointing.

Hypertension.—An epidemiologic survey on persons with high blood pressure without any evident cause was made by Morrison and Morris, who examined the blood pressure and family history of over 300 London bus drivers (*Lancet* 2:864, 1959). The blood pressure of about half the men fell within normal limits, that is, not higher than 150 mm. Hg systolic. The parents of this group of men lived to the age of 65 years or longer. By contrast the remaining group of drivers had parents who died between the ages of 40 and 64 years. These men had a bimodal distribution of blood pressure, about 50% having a peak at about 140 mm. Hg, while the others had a hypertensive peak at about 175 mm. Hg.

As would be expected the systolic pressure of all drivers rose as they grew older from an average of 147 mm. Hg for those 45 to 54 years of age to 158 mm. Hg for those 55 to 60; but the systolic pressures of the drivers in the 55-to-60-year age group whose parents had lived into old age showed the same distribution as those of their fellow workers of 45 to 54 years of age. Thus the average blood pressure of this group of older men did not rise significantly with age. The men with a parent who had died in the fifth or sixth decade of life could be classified into two groups, those in whom the first peak of blood pressure occurred when they were between the ages of 45 to 54 and ages 55 to 60 years and those whose blood pressure reached a second hypertensive peak when they were aged 55 to 60 years. The average rise of pressure during the fifth and sixth decade of the lives of these men seemed to be due not to any general or physiological rise but to the presence of a few subjects from families with high blood pressure. There were substantially more bus drivers than conductors with high blood pressure. The authors concluded that a rise in blood pressure is a disease, since it lowers the expectation of life. These studies showed that hypertension is a strongly hereditary syndrome possibly transmitted by a dominant gene.

Anthrax.—A committee set up to investigate anthrax reported (Report of the Committee of Inquiry on Anthrax, Command 846, Her Majesty's Stationery Office, 1959) that the incidence and mortality of this disease have fallen steeply since the beginning of the century. Reports of cases have dropped by 50%. The mortality has been greatly diminished due to effective chemotherapy, but the decline in anthrax has not been equal in all the industries using potentially infected materials. The disease has practically disappeared from industries in which most of the cases occurred in the past, that is, in those in which wool and hair are used. The biggest problem remains in industries in which hides and skin are handled. The industries in which these are used show no marked reduction in the incidence of external anthrax. The disease has occurred more frequently in those industries in which bones and bone meal are used. Half the fatal cases reported recently were due to handling these materials.

The committee recommended the control of imports and compulsory disinfection of such materials as goat hair, mohair, and cashmere. Materials should be sterilized, and special washing facilities should be provided where goods that may convey anthrax are handled. Workers who may be exposed to anthrax should be issued a card which they should show any doctor who sees them because of suspicious looking lesions, so that the doctor will consider the possibility that the patient has anthrax. The Factory Inspectorate and the Health Service should insure early reference of suspected cases to a doctor. Practitioners and hospitals in areas where workers might contract anthrax should be specially warned of the danger. Report of every case of anthrax should be made compulsory.

Life of the Blood Platelet.—The various methods used for estimating the lifespan of blood platelets before radioisotopes were used did not yield consistent results. Alfos and co-workers (*Lancet* 2:941, 1959) used a method that depends on diisopropylfluorophosphonate labeled with the radiophosphorus (DFP^{32}). This combines with the esterases in the platelets. The DFP^{32} was dissolved in peanut oil or isotonic sodium chloride solution, and 0.4 to 1.3 mg. were injected intramuscularly. Each milligram of material had an activity of between 45 and 200 μc. Blood was withdrawn by vein daily until the platelet activity was too low to measure. Platelets were separated from the blood by allowing it to stand for 30 to 60 minutes at 0 to 4 C, and dextran was added to sediment the erythrocytes. The supernatant plasma containing platelets and leukocytes was centrifuged. After repeated centrifugation the platelet count was determined and the specific radioactivity was estimated. The lifespan of the platelets was deducted from a plot of the DFP^{32} content, expressed in micrograms per 5×10^{12} platelets against time.

The life span of normal blood platelets was considered to be 8 to 10 days. The platelets in the blood of patients with the reticuloses (Hodgkin's disease and lymphosarcoma) were normal or slightly reduced. They were also slightly lower than normal in patients with localized malignant tumors. In patients with polycythemia the life span of the platelets was reduced when the peripheral platelet count was low and increased when it was high. The life span of the platelets was longer in patients with thrombocythemia, probably because of some mechanism for their removal which was impaired by the disease. The improvement in the clotting and the reduction of the platelet count after P^{32} therapy confirmed the intimate connection of the platelets with the bleeding tendency. The reduced life span of the platelets may result from reduced vitality because of interference with megakaryocytic maturation, increased function of the spleen, and the presence of autoantibodies.

Hospital Cross Infection.—Elek and co-workers reported a high incidence of whitlows in hospital nurses, which they attribute to cross-infection with the virus of herpes simplex (*Lancet* 2:871, 1959). Soon after the establishment of a hand clinic 54 cases were quickly reported among the nursing staff. The lesion started as a small area of irritation near the nail and progressed to deep vesicles which coalesced, giving a honeycombed appearance. The vesicles remained localized or spread by crops of fresh vesicles, leading to superficial tissue destruction which spread around the nail and fingertip or under the nail. At a later stage the appearance suggested a whitlow with pus under the cuticle. The lesions were painful, showed a tendency to spread for about 10 days, and took a further week or 10 days to resolve. When the lesions were incised they became secondarily infected with Staphylococcus pyogenes, usually of the type found in the patient's nose or of the type prevalent in the hospital. Bacteriological examination of unbroken vesicles showed the presence of the virus of herpes simplex in nearly every case.

Whitlows appear to be a hitherto unrecognized form of herpetic infection. In this outbreak the two possible sources were patients with herpetic lesions and symptomless salivary carriers of the herpetic virus. The nurses worked mainly in a neurosurgical unit, and it was found that after brain operations symptomless herpetic infection of the saliva of patients was comparatively common. These symptomless carriers were undoubtedly responsible for the soiling of the nurses' hands with infectious material. Almost half of the nurses in the hospital were found to be susceptible.

No Budget for Disease Prevention.—The Minister of Health admitted in the House of Commons that his Ministry had no funds to pay specialists for the prevention of disease. It can only pay for the cure of illness once it has occurred. This has resulted in a London hospital being short of funds. An Occupational Health Unit was opened at the Central Middlesex Hospital, London, three years ago, and the Nuffield Trust agreed to support it financially until the end of 1959. The unit was used by about 40 industrial organizations who were enthusiastic about its value to their workers. Research into the effects of work, fatigue, and working conditions on health was done. The Ministry of Health cannot support the unit financially. The matter has caused heated discussion in the House of Commons, where a Labor member urged amendment of the National Health Service Act to enable specialists to practice preventive as well as curative medicine.

Griseofulvin.—Beare and Mackenzie used griseofulvin to treat 19 children who had Microsporum canis infection (*Brit. M. J.* 2:1137, 1959). Infections of the scalp hair by M. canis offered certain advantages in a trial of a new drug since its effect could be observed by the fluorescence of infected hairs under Wood's light. Moreover, the condition is uninfluenced by topical treatment. The children were given 0.25 Gm. of griseofulvin three times daily, for an average period of 6 weeks (range 3 to 10 weeks). The affected area usually became completely nonfluorescent under Wood's light within three weeks of treatment. By contrast, cultures taken from hair samples, scales, and hair debris continued to be strongly positive, in some patients for many weeks. The criteria of eradication of infection were at least three consecutive negative cultures and negative microscopic findings at weekly intervals for 16 weeks. This long follow-up was necessary because one child was still infected after 14.5 weeks. Absence of fluorescence under Wood's light could not be accepted as evidence of freedom from infection. Using such strict criteria the results obtained with griseofulvin were not as favorable as those reported by other workers.

No toxic effects were seen from the drug, although it is said to be a mitotic poison when given in large doses to animals. Fungal invasion of hair ceases soon after the drug is given, but infected debris remains in the scalp and from it organisms can be recovered, in some cases three months or more after beginning treatment. As the condition cures itself spontaneously in this time the results obtained with griseofulvin cannot be considered particularly impressive. Indeed on this evidence it would appear that in itself the antibiotic is insufficient to cure ringworm of the scalp in a short period. It was thought that eradication of the organism from the scalp might be hastened if it were washed or scrubbed repeatedly and a fungicide applied locally as well as given orally.

Barlow and co-workers used griseofulvin to treat 34 patients with persistent fungal infections of the skin (*Brit. M. J.* 2:1141, 1959). The infecting organisms were Trichophyton rubrum, Trichophyton verrucosum, Trichophyton mentagrophytes, and Candida albicans. No appreciable hematological effect was noted, but a few patients complained of headache, nausea, and malaise, and five patients developed an erythematous rash. Three patients were unable to tolerate the drug. Griseofulvin was ineffective against infection with C. albicans, Malassezia furfur, and T. verrucosum, but it did benefit patients infected with other dermatophytes, including T. rubrum. While most patients improved, in only one was the infection eradicated. Since griseofulvin is fungistatic and not fungicidal it may be necessary for the adequate treatment of nail infections to give the antibiotic for long periods while the nail grows out. This may take a year for infections of the nail of the big toe.

Treatment of Tetanus with Chlorpromazine.—The successful treatment of tetanus with chlorpromazine, first reported by Laurence, was confirmed by Shanker and Mehrotra (*Brit. M. J.* 2:1150, 1959). This drug, besides inhibiting motor activity and diminishing the tone of skeletal muscle, has a sedative and tranquilizing action. In addition, it potentiates the action of hypnotics and sedatives. These properties make it particularly suitable for the relief of the muscle spasms of tetanus. The authors treated 30 patients who had tetanus, one half being given chlorpromazine and the other half paraldehyde. The general nursing care and the use of antitoxin was the same in both groups. All patients were given penicillin prophylactically. Reflex spasms were dramatically controlled within 30 minutes and did not recur for at least four hours after an injection of chlorpromazine. There were three deaths in the group treated with chlorpromazine and seven in the control group. The results were even better than these figures would suggest, as there were more serious cases in the chlorpromazine-treated group than in the controls. A cure rate of 92% was recorded in the chlorpromazine-treated patients who survived for more than 24 hours. The corresponding figure for the control group was 62.6%.

Anti-G Suit for Hypotension.—A 67-year-old woman suffering from cerebral anoxia due to persistent hypotension was treated by means of a jet pilot's anti-G suit. The woman had been bed-ridden because if she stood or even sat up she blacked out from the reduced flow of blood to the head. The pressure of the G-suit around the legs and waist redistributed peripheral blood to the upper part of the body. After putting on the suit the patient was able to stand and sit without loss of consciousness for the first time in six months.

Blood Pressure and Age.—Five years ago Miall determined the blood pressure in a random sample of the general population and all the first degree relatives of the population of Rhondda Fach in Wales. He has followed this up to examine the effect of age and other factors (*Brit. M. J.* 2:1204, 1959). Reexaminations were made under identical conditions on 1,114 (99.6%) of the 1,119 subjects seen originally and still resident within 25 miles of the valley. It was found that over the five-year period the blood pressure of the women remained the same, but that of the men increased in all age groups. The results suggest that when full allowance is made for age, arterial pressure may be increasing in middle-aged men.

This trend is occurring to a greater extent in men previously engaged in heavy work, although they still have lower pressures than those previously in light occupations. The differences in the mean systolic and diastolic pressures at 45 years of age between men in light occupations and those in heavy occupations were 10 and 8 mm. Hg respectively. Blood pressure was found to correlate with family size in both the men and the women; the larger the family the lower the pressure. This trend was clear-cut only in the reproductive age, which was taken to be 15 to 45 for women and 15 to 50 for men. In several of the age groups the mean arterial pressure recorded in the follow-up period fell in the women who had had children, whereas it did not fall in those who had not.

The effect of taking added salt in the diet was studied. In view of the effect of salt restriction on the blood pressure of hypertensives it was expected that a high salt intake would be associated with a higher arterial pressure than a low salt intake. This was not so. In fact the converse was found, women who added salt to their cooked meals being found to have lower blood pressures and smaller pulse pressures than those who did not. The former group were also lighter. No comparable differences were found in the men.

Infant Feeding.—In a report by the Medical Research Council (Weight Gains, Serum Protein Levels, and Health of Breast Fed and Artificially Fed Infants, M. R. C. Report 296, Her Majesty's Stationery Office, London, 1959) normal standards of weight and hemoglobin, serum albumin, and globulin levels were established for the first 18 months of life from studies on 521 full-term and 223 premature infants. The artificially fed infants were given full cream dried milk made up with water and added sugar. The incidence of infection was found to be the same in both breast fed and artificially fed infants, and there was no significant difference in the weights of the two groups. It was concluded that breast milk is inadequate for premature infants, whose protein needs cannot be satisfied with it.

Serum albumin and globulin levels in the normal infant were found to be unaffected by the type of feeding. The serum gamma-globulin level was found to be higher at birth than in adults, but it dropped shortly after birth and reached its lowest level in the fourth or fifth month. Part of the gamma globulin is synthesized by the fetus, and this synthesis continues after birth. Dilution in an expanding plasma volume may account for the falling gamma-globulin level, which may remain relatively constant during the first three months of life. Although the report recognized that there was no physiological or nutritional advantage in breast feeding, it pointed out that it is highly desirable because of the natural emotional relationship that it establishes between mother and child.

Postoperative Venous Thrombosis.—Pulmonary embolism and thrombosis of deep veins of the legs are relatively common causes of illness and death in those over 50 years of age confined to bed for any length of time after operations or for illness. Sevitt and Gallagher stated that at the Birmingham Accident Hospital pulmonary embolism was found at 20% of autopsies and was the cause of death in 40 to 50% of elderly patients who died from a fracture of the femur, tibia, or pelvis. In the same hospital thrombosis of the deep veins of the leg occurred in 60% of fatally injured patients without a pulmonary embolism. As thrombosis is a silent process and widespread postoperatively in elderly persons, the authors made a controlled clinical trial to observe the effect of the anticoagulant phenindione, when given prophylactically, on the incidence of postoperative thrombosis and pulmonary embolism in the elderly (*Lancet* 2:981, 1959). The trial was restricted to patients over 55 years of age with either a subcapital or intertrochanteric fracture of the femur because of the high incidence of embolism and thrombosis in such patients. From the point of view of a controlled trial they formed a homogenous group with a fairly common, single, and almost standard trauma, similar age and sex distribution, and a high death rate, which would serve as an effective yardstick in assessing the value of the prophylactic action of an anticoagulant.

In a series of 300 patients phenindione was given to half and the rest served as controls. The drug was given on the day of admission or before the operation for a mean period of five weeks and generally until the patient was ambulant. In a few the administration of the drug was continued after the patient left the hospital. The initial dose of phenindione was 200 mg., followed the next day by 100 mg., and subsequently by 25 to 75 mg. daily. Dosage was controlled by the one-stage plasma prothrombin level (Quick), which was maintained at between 15 and 30% of the normal value. Urine and feces were tested for blood if the prothrombin fell to undesirable levels. Patients in special danger of hemorrhage, such as those suffering from melena, hematemesis, hematuria, recent peptic ulcers, or hemoptysis were not given phenindione. The diagnostic criteria used to detect thrombosis or embolism were the same in the treated and control groups. Patients were followed up for at least three months from the time of the fracture, and in fatal cases an autopsy was performed with careful dissection of the lower venous tree, whenever possible.

There were 43 cases of clinically diagnosable thrombosis in the control series (29%) compared with only 4 cases in the phenindione-treated series

(3%), a reduction of over 90% in frequency. The average inpatient stay of the survivors with clinical thrombosis was 54 days in the control series and 42 days in those who received phenindione. Thus, prophylaxis with the latter shortened bed rest and saved lives. None of the phenindione-treated patients developed nonfatal clinical embolism whereas eight of the controls did. A fatal major embolism was found in 17 of the patients in the control series and in 2 of the phenindione-treated group. The two latter deaths occurred after treatment had been discontinued, so that they were not really failures of prophylaxis. No patient had a fatal thrombosis while taking phenindione.

Even more conclusive was a comparison of the frequency of thrombosis in the deep veins of the lower limbs at autopsy. Significant or extensive thrombosis was found in 29 of the 35 control patients (83%) compared with only 3 of the 21 phenindione-treated patients examined (14%). Autopsy revealed that almost 40% of the patients in the control series had developed some form of thromboembolic disease other than deep vein thrombosis, while only 4.7% of the phenindione-treated patients had cases of these diseases, all of which could be explained. The evidence indicated that phenindione effectively prevented thrombosis in veins and eliminated the risk of pulmonary embolism in patients under its influence, provided it was given early, for sufficient time, and under laboratory control.

Drug Publicity.—In a letter to the *British Medical Journal* a group of physicians in Edinburgh, led by Prof. J. W. Crofton, protested strongly against the mounting publicity given to new drugs and new treatments in the national press and over the radio and television. In particular they object to that given to a new treatment for chronic bronchitis with a preparation containing finely divided chymotrypsin and isoprenaline. A press conference was held in London recently by the company marketing it. Press representatives were informed that 60 general practitioners in various industrial areas had tested this preparation. Two of the doctors concerned related their experiences in treating over 200 chronic bronchitics, in whom excellent results were obtained. This press and radio publicity resulted in many chronic bronchitics demanding the new treatment for their complaint.

Prof. Crofton and colleagues considered that the claims made were extravagant on the evidence available. They questioned the statement of the manufacturers that a mucolytic enzyme combined with a bronchodilator produced satisfactory improvement in 71 to 92% of the chronic bronchitics treated. The design of the trial was faulty. It was done in late spring and early summer, when bronchitics improve spontaneously and it was inadequately controlled. In this kind of advertising a pseudoscientific façade conceals an unsound approach to the testing of a new drug. The letter objected to radio and press advertising of new remedies because these media are regarded by the public as authoritative. Many patients who heard the broadcast or read the press reports approached the writers full of hope about the new treatment and begged to have it given to them. These physicians felt compelled to give it a trial in several patients who would have otherwise complained bitterly that they were being denied the benefit of a major therapeutic advance. None of those given the treatment received any noticeable benefit. The doctors urged that the matter be brought to the attention of the British Broadcasting Corporation.

In an editorial the *British Medical Journal* pointed out there was no longer any excuse for any firm to market a product for which a therapeutic advance is claimed until it has been submitted to a carefully conducted controlled clinical trial to establish the claims made for it. In the long run it will be commercially more profitable to the pharmaceutical industry to conduct such trials than to sell poorly tested new drugs in the market place.

Response to Vasodilator Drugs.—Gillespie questioned the value of vasodilator drugs in the treatment of obliterative vascular disease (*Lancet* 2:995, 1959). In patients with this condition he examined their effect on blood-flow in the foot and in calf muscles, their value in augmenting the effect of sympathectomy, and their use in forecasting the result of lumbar sympathectomy. As the blood flow in the foot and calf can be measured the value of vasodilators can be readily assessed. Blood flow in the foot and calf of patients with and without obliterative arterial disease and before and after administering the vasodilator was measured by venous-occlusion plethysmography with water-filled plethysmographs in a constant-temperature laboratory. The drugs tested were tolazoline, phenoxybenzamine, chlorpromazine, and promazine.

Vasodilators increased blood flow to the feet of healthy subjects, but the response in limbs with occluded arteries was different. In patients with unilateral occlusion, vasodilators increased blood flow in the healthy foot but decreased it in most cases in the foot with occluded arteries. Intermittent claudication is prone to such spontaneous variations in severity that the result of clinical drug trials must be interpreted with caution. If vasodilators are to relieve claudication they must increase the blood flow in the muscles. Gillespie found that they decreased the blood flow by 4% in healthy subjects and up to 26% in patients with obliterative vascular disease. The effect of vasodilators on the blood flow of 29 sympathectomized feet was examined. In 25 limbs there was no increase. In some a decrease occurred. The response to vasodilator drugs gave no indication of the probable effect of sympathectomy in occlusive vascular disease, and was of no value as a preoperative test.

CORRESPONDENCE

PEPTIC ULCERS IN CHILDREN

To the Editor:—I am writing with regard to the comment, entitled "Peptic Ulcers in Children," which appeared in THE JOURNAL, Dec. 5, 1959, page 1990. Dr. Tudor states that he is "establishing a registry of children who have peptic ulcers" and requests "anyone who knows of child patients with peptic ulcer, diagnosed either post mortem or roentgenographically," to send him the pertinent data. I wonder if Dr. Tudor is aware how equivocal a roentgenographic diagnosis of peptic ulcer in children is. If he would consult radiologists at any outstanding children's hospital in the country, he would discover that the roentgenographic diagnosis of peptic ulcer in children is extremely rare, frequent diagnosis by less experienced examiners notwithstanding.

Among radiologists familiar with pediatric gastroenterology, such findings as spasm, hypersecretion, and prominent rugae, which are often used to establish the diagnosis, are considered normal in children. It is doubtful whether the establishment of a registry based on equivocal cases would be of any value.

E. J. KEEFFE, M.D.
St. Joseph Mercy Hospital
Pontiac, Mich.

To the Editor:—I appreciate the letter from Dr. Keeffe concerning the difficulties in the diagnosis of peptic ulcers in children. I am aware of the difficulty, since I have been working with this problem for 11 years. The four radiologists on the staff of my clinic are experienced in pediatric radiology. Our radiology residents spend a portion of their time in pediatric radiology at Childrens' Hospital, in Cincinnati. A diagnosis of peptic ulcer is not made unless an ulcer crater can be demonstrated. To minimize exposure of the patient, the fluoroscopic time is sharply limited and reliance is placed on multiple spot films in various projections, including double-contrast examination of the duodenal bulb. Ordinarily, 8 to 12 spot films and 4 roentgenograms are taken during the stomach examination. The best detail is obtained with use of water-soluble contrast agents.

In the last 11 years, over 90 pediatric peptic ulcers have been demonstrated. The youngest patient was one day old. Follow-up examinations at 6 to 12 weeks in the patient with gastric ulcer and in selected patients with duodenal ulcer have demonstrated satisfactory healing. The chief of the department of radiology at the children's hospital in Stockholm reviewed the films during a visit in 1957 and agreed with our findings. We would not make a diagnosis of peptic ulcer from such secondary signs of ulceration as spasm, hypersecretion, or prominent and irregular rugal folds.

ROBERT B. TUDOR, M.D.
Quain & Ramstad Clinic
Bismarck, N. D.

AVICENNA

To the Editor:—In THE JOURNAL, Aug. 4, 1945, the filler on page 1003 cites a common error, that of calling Avicenna a "most distinguished Arab physician." Avicenna, or Abu Ali al Hussein ibn Sina, was a Persian, born of Persian parents in 980 A. D., in Khormisan, near Bukhara, then the Persian capital but now in the U. S. S. R. He became physician to several Iranian kings and finally minister to one of them. Of his 283 books, some were in Persian but most of them in Arabic, the language of science at that time, as Latin was to be later. (Yahya Mahdavi: Bibliographie D'lbn Sina, University Tehran, no. 206, in Persian.) Ibn Sina died in 1037 A. D. in Hamadan, the Ecbatana of Alexander's time. An imposing memorial honors him there.

MANOUCHEHR NADIMI, M.D.
Shiraz Medical Center
Nemazee Hospital
Shiraz, Iran.

EDITOR'S NOTE: Other items pertaining to Avicenna have appeared in the Correspondence section of THE JOURNAL, May 24, 1952, page 390, and Nov. 1, 1952, page 951.

SHOOTING ACCIDENTS

To the Editor:—The news item, "Report On Shooting Accidents," which appeared in THE JOURNAL, Dec. 19, page 2232, is an excellent example of statistical accuracy that can be misused to substantiate claims of anti-gun enthusiasts that are completely unwarranted by the facts.

The fact that persons aged 15 to 19 constitute only 3% of the total population of the United States, while accounting for about 16% of those fatally injured in firearm accidents, is somewhat irrelevant to the question of whether or not these users might be capable of handling firearms. Much more useful data would be the frequency of accidents in 15-to-19-year-olds in proportion to the total number of man-hours spent in hunting with guns. It appears extremely unlikely that 3% of women or of elderly persons in the total population spend much time with firearms. For that reason, too, a high accident rate would be expected in young men, even though they use the same amount of care and precaution as do other segments of the population.

I recognize that this news item was simply reported from an outside source, but I believe care should be taken in disseminating this sort of information, to prevent its becoming available to persons who will misconstrue the facts and use them to their advantage.

Charles Watkins, M.D.
Louisiana State University
1542 Tulane Ave.
New Orleans 12.

ELEMENTS OF STYLE

To the Editor:—I have read the editorial, "Elements of Style," in The Journal, Jan. 23, page 345. Naturally, I am flattered. I must accept the compliment with some reservation, however, because as a matter of fact I have on occasion made a number of revisions or drafts before I have been satisfied with what I have written. It seems to me that this is bound to be so.

Paul D. White, M.D.
264 Beacon St.
Boston.

I suspect that even a medical Winston Churchill finds it necessary to revise and rewrite some manuscripts.—Ed.

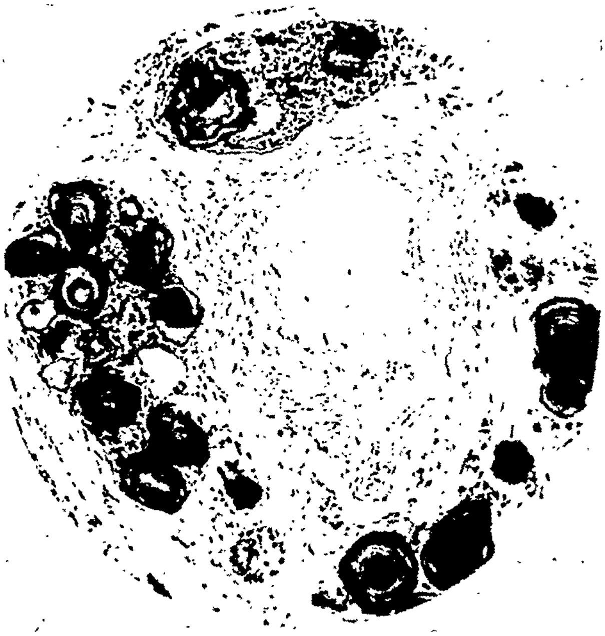
PSAMMOMA BODIES IN CANCER OF LUNG

To the Editor:—In their article on psammoma bodies and cancer of the thyroid (abstracted in The Journal, Nov. 28, page 1901) Klink and Winship stated that these bodies occur in a large percentage of patients with cancer of the thyroid and that "A biopsy specimen of a lung tumor that contains psammoma bodies should suggest the thyroid as a possible primary site." Their statement implies that similar calcific concrements are not apt to be found in patients with cancer of the lung.

Such bodies were found in a patient with primary cancer of the lung, a man aged 26 years whose illness started abruptly with an uncontrollable hiccough. Roentgenologic examination revealed, at the base of the right lung, a well circumscribed dense shadow which merged with the diaphragm. Bronchoscopic examination gave a negative result and the laboratory data were noncontributory. The patient recovered from his hiccough after three days and complained of no other symptoms. The diagnosis of a benign neoplasm was made. The patient was discharged and instructed to report for periodic reexamination.

He remained asymptomatic for about six years. During this time, x-ray examinations failed to show any changes in the dense basal shadow of the right lung, but at the end of this period he had begun coughing and expectorating a large amount of sputum. He complained of mild pain in his chest, loss of weight, and growing weakness. A roentgenogram of the right lung showed an area of density at the base, about 6 cm. in diameter, and multiple nodular densities scattered throughout the lung. The left lung showed several metastases. The patient died about six and one-half years after the onset of symptoms, with signs of cerebral metastases.

The autopsy revealed an epidermoid carcinoma (lymphangiotic type) of the right lung, with metastases to the left lung and to the bronchial lymph nodes. On histological examination the nodular densities observed in the roentgenogram were found to be hyalinized tissue. They contained entrapped cancer cells and round, concentrically laminated concretions, namely, psammoma bodies (calcospherites or microliths). The calcific bodies were confined to the perivascular spaces of small and large pulmonary vessels (see figure), along which the cancer had spread. They were not found in the metastases to the left lung but were present in the metastases to the bronchial lymph nodes. They were not found in the lumens of the air sacs. This case serves to illustrate an instance in which psammoma bodies were found in a primary epidermoid cancer of the lung.



Psammoma bodies and cancer cells in perivascular spaces of pulmonary vein.

B. M. Fried, M.D.
1560 Grand Concourse
New York 57.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Tuberous Sclerosis: A Report of 16 Cases in Two Family Trees Revealing Genetic Dominance. D. Marshall, G. B. Saul and E. Sachs Jr. New England J. Med. 261:1102-1105 (Nov. 26) 1959 [Boston].

The authors' review of the literature on tuberous sclerosis makes it evident that this condition, with the classic triad of mental deficiency, epilepsy, and adenoma sebaceum, is a widespread tissue dysplasia of unknown causation involving all the primitive germ layers. The authors report tuberous sclerosis in a 24-year-old woman and in a 16-year-old youth. Both patients were first seen by ophthalmologists because of diplopia. In the woman, it was the x-ray finding of calcific densities in the brain that first suggested the diagnosis. A ventriculogram revealed intraventricular pressure of over 600 mm. and symmetrical dilatation of both lateral ventricles as well as of the 3rd and 4th ventricles. A ventriculomastoidostomy was done on the right side. After several unsuccessful attempts to maintain patency of the ventriculomastoidostomy, a transventriculofrontal craniotomy on the right side was done, which showed the entire right lateral ventricle and the 3rd ventricle filled with a red, vascular tumor. The tumor was removed. The patient died on the 5th postoperative day. At autopsy, considerable softening and necrosis extending into the hypothalamus and caudate nucleus were observed. Other findings included a defect of the interatrial septum, a leiomyoma of the kidney, and fibromas of the heart, liver, vaginal wall, and lungs. The brain tumor was an ependymoma, grade 3. The family history revealed 12 members in 3 generations with tuberous sclerosis, 7 of whom were severely affected and 5 were mildly affected. Examination of the second patient revealed bilateral papilledema, adenoma sebaceum of the face, café-au-lait spots, patchy leukoderma, and periungual fibromas. Ventriculography showed a tumor of the 3rd ventricle, which was removed surgically. Microscopic examination of the operative specimen revealed an astrocytoma. The patient died on the 10th postoperative day. The family history revealed that the patient's mother had tuberous sclerosis with adenoma sebaceum of the face and intracranial calcification and seizures. She too had an astrocytoma of the 3rd ventricle, which had been removed in 1932, and she is still living. The patient's grandfather also had had adenoma sebaceum and subungual fibromas.

Although some of the family members of the first patient could be described as showing severe generalized involvement, few exhibited the classic triad of tuberous sclerosis. More often only one or two of the classic findings were present, usually in association with some other morbid condition. The genetic significance of making the diagnosis of tuberous sclerosis in persons who have only the "forme fruste" type of the disease is pointed out, and it is emphasized that any medical specialist may be the first to see such a patient. This series brings to light a group of patients who have tuberous sclerosis with the relatively rare association of brain tumors. The necessity of following children of involved parents for subsequent development of signs or symptoms of tuberous sclerosis is emphasized. The genetics of the lineage in the families of the 2 patients are discussed, and the mode of inheritance is shown to be by a dominant gene that can be affected by an independent pair of modifying genes.

Acute Anoxic Cardiac Failure in Pulmonary Heart-Disease. G. Kellaway. Lancet 2:768-773 (Nov. 7) 1959 [London].

The author reports on 32 men and 12 women with acute anoxic cardiac failure, due to pulmonary heart disease as the sole causative factor, and right ventricular strain, as revealed by the electrocardiogram, who were admitted to the department of cardiology of the Royal Infirmary in Edinburgh. These patients represented 13% of 334 patients who were admitted to this hospital with cardiac failure uncomplicated by other cardiovascular disease. For at least 3 days the patients were maintained in an oxygen tent. Apart from treatment with mechanical respirators, there is no readily available method of restoring arterial oxygen levels to normal without the danger of carbon dioxide narcosis. The author's method of administering continuous oxygen therapy, without permitting carbon dioxide narcosis to supervene, consisted of intramuscular injections of 5 cc. of nikethamide and of 30 mg. of amiphenazole every 2 hours. The injections of nikethamide and

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The place of publication of the periodical appears in brackets preceding each abstract.

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amiphenazole were alternated, so that the patients received a respiratory stimulant every hour. Signs of carbon dioxide narcosis were considered as an indication for more frequent doses of respiratory stimulants. Antibiotics were given to help overcome the respiratory infection. Sedation was necessary in all the patients, and meperidine (Demerol) was given in doses of 50 to 150 mg. Those with clinical evidence of moderately severe carbon dioxide narcosis also were given 2 mg. of levallorphan per 100 mg. of meperidine to counteract possible depression of the respiratory center.

Eighteen of the 44 patients, with an average age of 60 years, were treated according to this method. Five patients died. Satisfactory oxygenation and clinical improvement were evident in 13 patients within 3 days of the institution of treatment, and usually administration of respiratory stimulants was unnecessary after the 5th day. Oliguria persisted for several days after arterial oxygen saturation was raised to normal levels. During this period edema increased despite clinical improvement. The results suggest that the administration of oxygen should be continued until diuresis begins. When discharged from hospital, all 13 patients were free from cardiac failure. The absence of deaths due to carbon dioxide narcosis and the improvement in immediate and more distant prognosis suggest that this is a good method of managing these patients.

Hypercalciuria in Hepatolenticular Degeneration (Wilson's Disease). R. B. Litin, R. V. Randall and others. Am. J. M. Sc. 238:614-620 (Nov.) 1959 [Philadelphia].

Five patients with hepatolenticular degeneration (Wilson's disease) were observed at the Mayo Clinic. The diagnosis of this disease had been established by the findings of neurological manifestations, typical Kayser-Fleischer rings, and increased urinary excretion of copper and alpha-amino nitrogen. There was no familial history of hepatolenticular degeneration for any of the patients, and none of them had received treatment for this disease for 1 to 4 months prior to this study. The urinary excretion of calcium was measured in each patient over a 3-day period, during which the patients were given a diet containing a known amount of calcium. Three successive specimens of urine were collected from each patient over 24-hour periods, and analyzed the day the collection was completed.

Under the diet used in this study, a value of urinary calcium above 170 mg. per 24 hours can usually be considered to be abnormal. By this criterion, 4 of the 5 patients had hypercalciuria. One patient had nephrocalcinosis and a history of nephrolithiasis, and another had a stone in the left kidney. Excretory urograms in 2 of the other patients were normal. The cause of the hypercalciuria was not determined. The authors suggest that hypercalciuria in hepatolenticular degeneration may represent another tubular defect inherent to the disease.

Clinical Observations Regarding Xanthelasma. J. B. Vacca, W. A. Knight Jr. and G. O. Broun Sr. Ann. Int. Med. 51:1019-1031 (Nov.) 1959 [Lancaster, Pa.]

Xanthelasma or xanthoma palpebrarum has been reported more frequently than any other type of cutaneous xanthoma. It has been noted to occur in many types of xanthomatosis, especially with xanthoma tuberosum and xanthoma disseminatum, but is believed not to occur with the xanthomatosis associated with essential hyperlipemia. In order to determine the clinical significance of xanthelasma, 51 consecutive persons (patients, relatives of patients, visitors, employees, outpatients) with xanthelasma observed in the environs of a general hospital by members of the house staff, student body, and attending staff were examined by one of the authors during a period of about 18 months. A complete history and a physical examination were obtained in all 51 persons, with particular emphasis on the following: how long the xanthelasma had been present; size of the xanthelasma; presence of xanthoma elsewhere; evidence of angina pectoris, myocardial infarction, congestive heart failure, heart murmurs, hypertension, or diabetes mellitus; menstrual history; evaluation of retinal, cerebral, and peripheral vascular status; height and weight; nutritional status; family history of xanthelasma or xanthoma elsewhere, coronary artery disease, and vascular disease generally.

Thirteen of the 35 women in the group of 51 persons were more than 40 lb. (18.1 kg.) overweight, whereas only 1 of the 16 men was that much overweight. Of the 35 patients who were adequately tested, 12 had clinical or latent diabetes mellitus of the adult type. Thirty-one of the 35 women with xanthelasma were postmenopausal at the time of this study, and 9 of these had had their menopause before the age of 45 years.

Seventy-three per cent of the entire group of 51 persons had a cholesterol level greater than 300 mg. per 100 cc., and 79% of those tested had mild to moderate elevations of total blood lipids. Evidence of coronary artery disease was present in 69% of the men and in 43% of the women. Peripheral vascular disease occurred in 20% and cerebrovascular disease in 8% of the entire group of patients. The occurrence of cachexia or a wasting disease in a person with xanthelasma was associated with a lower elevation of blood lipids. There were indications of a general relationship between the size of the xanthelasma and the cholesterol level. A striking variation of serum cholesterol levels was observed in many of the patients. The degree of fluctuation seemed to be related to the mean cholesterol level. A family history of xanthoma (including xanthelasma) or of prominent vascular disease was obtained in a minority of the persons studied. There were 5 persons in whom there was a definite family history of xanthelasma in association with cardiovascular disease; in addition, one person's brother was known to have tendon xanthoma and to have died in middle age of a myocardial infarction. Besides these, there were 3 persons who had a striking family history of cardiovascular disease without any definite knowledge of the presence of xanthelasma or other xanthoma in the affected relatives.

Takayashu's Syndrome: Pulseless Disease. P. Kølle-Jørgensen. Ugesk. læger 121:1694-1695 (Oct. 29) 1959 (In Danish) [Copenhagen].

Sixteen cases of pulseless disease (Takayashu's disease) or arteritis brachiocephalica have been reported from Scandinavia, 3 of them from Denmark. The etiology is not known. Increased sedimentation reaction is thought to be a constant feature in the disease, which is marked by a progressive closing of the large arteries that proceed from the aortic arch. Pathologically, there are fibrous hyperplasia of the intima and chronic infection in the media and the intima. The symptomatology varies, depending on the arteries affected and the degree of closure. The disease occurs almost exclusively in women; only 3 cases in men have been reported in the European literature. The prognosis is unfavorable, but the course is often prolonged. The case described is unusual in being unilateral and in a man. Examination showed increased sedimentation reaction and absence of pulsation in the right arm and on the right side of the neck. The diagnosis was verified by aortography. Examination of the serum protein showed normal conditions. As the patient's main difficulty was due to thromboses, regarded as secondary to the arteritis, ambulant long-term anticoagulant treatment was instituted.

Results of Treatment of Malignant Hypertension: A Seven-Year Experience in 94 Cases. M. Harington, P. Kincaid-Smith and J. McMichael. Brit. M. J. 2:969-980 (Nov. 14) 1959 [London].

Eight years have elapsed since the introduction of ganglion-blocking agents in the treatment of severe hypertension. The present report deals with malignant hypertension under this treatment, and the course of the treated cases is compared with a control series from the same London hospital over the period 1935-1956. The series comprises 82 patients with malignant hypertension. This total includes all patients seen at this hospital in the years 1951-1957, inclusive, in whom malignant hypertension was diagnosed and in whom treatment with ganglion-blocking drugs was attempted (12 were not treated because they were in the terminal stages when admitted).

The expectation of life of the treated patients was increased by a factor of 6 to 8 times that expected from the control series. Prolonged survival was particularly seen in patients whose renal function was normal or only slightly impaired. Death was most frequently due to uremia; death from heart failure was considerably diminished in the treated group. The benefits of treatment were most pronounced on retinitis and in heart failure. Improvement in the electrocardiogram was seen in one-third of the cases; reduction in cardiac size occurred somewhat less frequently.

Renal function tended to remain stationary or to improve slightly in patients with an initial blood urea level below 80 mg. per 100 cc.; where renal impairment was more severe than this, progressive deterioration was the rule. Patients with neurological complications did not derive much benefit from treatment. Atherosclerosis was a limiting factor in the success of treatment, particularly in older patients. A survey of the histological lesions in the kidneys showed that, after treatment with hypotensive drugs, the main changes were a conversion of cellular intimal hyperplasia in the interlobular arteries to fibrous intimal thickening and a "healing" of fibrinoid degeneration to hyaline and fibrous tissue. There was some correlation between the degree of narrowing of the interlobular arteries at the start of treatment and prognosis.

Whirlpool-Induced Purpura in Anaphylactoid Purpura. H. Hoefle Jr. and R. C. Williams Jr. Am. J. M. Sc. 238:610-613 (Nov.) 1959 [Philadelphia].

A case of anaphylactoid purpura presenting unusual diagnostic features is reported. The patient, a 23-year-old Air Force staff sergeant, was admitted to the USAF Hospital in Wiesbaden, Germany, complaining of pain and stiffness in the left hip after a fall. Laboratory examinations, roentgenograms, and electrograms were normal. In spite of therapy with bed rest, aspirin, and physical therapy, the patient had a temperature of 100 to 100.6 F (37.7 to 38 C) and pain, swelling, heat, and stiffness of the joints. These symptoms gradually abated, but petechiae and purpuric spots appeared on the anterior surface of the legs between the knees and ankles. Repeated blood counts, bleeding and clotting times, and Rumpel-Leede tourniquet tests were within normal limits. The patient was transferred to another hospital because of petechiae and continued to suffer from moderate arthralgia. Five weeks after the onset of the disease, a whirlpool treatment was added to the salicylate therapy. Shortly after immersing his legs in the whirlpool bath, the patient noted a recurrence of petechiae over his lower legs. The same occurred with additional baths. Concomitantly the results of all blood examinations were within normal limits.

It was felt that this patient had Henoch-Schönlein's syndrome, or anaphylactoid purpura associated with mild and recurrent arthralgia. He was treated symptomatically with salicylates and graduated exercises, and recovered his joint function over the next 6 weeks. During this period the petechiae also subsided. The patient returned to duty and during the next 5 months had no recurrence of symptoms, not even with repeated whirlpool immersion. It was concluded that the combination of heat and mechanical trauma induced purpura in the capillary beds exposed to the whirlpool bath. This effect is not present in normal subjects and was not present in the patient after recovery from his acute illness. The findings suggest that whirlpool bath immersion may be of value in assessing capillary fragility when other tests of capillary integrity are normal.

Value of Laboratory Tests in the Diagnosis of Anicteric Metastatic Hepatopathies. A. J. Piccaluga, R. M. Laplacette and others. Prensa méd. argent. 46:1174-1177 (May 8) 1959 (In Spanish) [Buenos Aires].

Fourteen anicteric patients with metastatic tumors of the liver underwent laboratory tests of bilirubinemia, cholesteremia, alkaline phosphatasemia, turbidity, and flocculation as well as paper electrophoresis. The diagnosis of the primary tumor was established surgically in 7 patients, by puncture biopsy in 6, and clinically in 1. Only the findings of the first examination of the 14 patients are considered in this report. The most marked changes were those in phosphatasemia, albuminemia, and globulinemia. The phosphatasemia values exceeded 6 Bodansky units in 10 patients, and exceeded 20 units in 7. Hypoalbuminemia was found in 93% of the patients. There was an increase in alpha-1 globulin and a marked increase in alpha-2 globulin which reached above normal values in all 14 patients studied. The authors conclude that the determination of alkaline phosphatasemia and the findings of paper electrophoresis have a definite value in the detection of secondary tumors of the liver. One of the causes of the elevation in alkaline phosphatasemia is the compression and distortion of the intrahepatic biliary ducts by tumoral nodules.

Factors Controlling Hemopoiesis: Experimental Observations on Their Role in Polycythemia Vera. J. W. Linman, F. H. Bethell and M. J. Long. Ann. Int. Med. 51:1003-1018 (Nov.) 1959 [Lancaster, Pa.].

Until recently little was known concerning the manner in which erythrocytic equilibrium was maintained or restored. During the last few years, studies in many laboratories have established the existence of a humoral erythropoietic regulatory mechanism, and evidence is now available which suggests that the formation of other hemic elements may be subject to similar controlling factors. Studies carried out by the authors indicate that 2 humoral factors exert basic regulatory control over erythropoiesis. A relatively thermolabile, ether-insoluble agent augments hemoglobin synthesis, whereas a thermostable, ether-soluble factor appears to govern the mitotic or proliferative activity of erythrocytic precursors. This humoral mechanism most likely constitutes the primary erythropoietic stimulus, and is apparently responsible for the maintenance of the normal erythroid steady state and for the accelerated erythropoiesis which accompanies hypoxic and certain types of anemic hypoxia. The presence of enhanced plasma erythropoietic activity in patients with polycythemia vera, which occurs in the absence of hypoxia and persists irrespective of the institution of specific myelosuppressive therapy, supports the thesis that the humoral factors are of etiological importance in this disorder.

The ether-soluble or thermostable fractions of plasmas from patients with polycythemia vera also possess thrombocytic and granulocytic stimulatory activity. It is suggested that batyl alcohol, a substance which also induces erythrocytosis, thrombocytosis, and granulocytosis in normal rats, may be closely related to the thermostable, ether-soluble plasma factor. Although the precise significance of the hemopoietic effects of batyl alcohol and of the plasmas of patients with polycythemia vera is still speculative, observations lend credence to the theory that all aspects of hemopoiesis are under humoral regulatory control. A single agent may affect (although not to the exclusion of other mechanisms) the formation of all hemic elements, and may explain the thrombocytosis and leukocytosis associated with such conditions as polycythemia vera, acute hemorrhage, and hemolysis. Further study of the factors controlling hemopoiesis should clarify certain currently obscure hematological disorders and responses.

Marfan's Syndrome and the Weill-Marchesani Syndrome in the S. Family. D. Bowers. Ann. Int. Med. 51:1049-1070 (Nov.) 1959 [Lancaster, Pa.].

The author mentions Marfan's description of dolichostenomelia in 1896 and also Archad's emphasis on the spidery extremities, with the term "arachnodactyly," and Boerger's report on the association of dislocated ocular lenses with the arachnodactyly. The hereditary transmission of the abnormalities referred to as Marfan's syndrome has been pointed out, and a number of families, each containing multiple cases of the syndrome, have been described. The S. family is believed to have contained at least 33 affected members in 6 generations. The skeletal, ocular, cardiovascular, and hereditary characteristics of Marfan's syndrome are all well exemplified in this family.

The first generation of the S. family was a young couple who emigrated from Baden in southern Germany to a county in Ontario, Canada, about 1853 or 1854. The diagram of the genealogical tree of the S. family indicates the affected members. The histories of the living patients and of the 17 who have died are presented. The understanding of Marfan's syndrome has been hampered by ignorance of the criteria necessary for its diagnosis. Spidery extremities have been accepted by certain authors as a sufficient condition for this diagnosis, but it has been pointed out that long, slender limbs may also occur in eunuchoidism or as an anthropological variant. Lens dislocation or aortic medionecrosis, as isolated abnormalities, should also not be accepted as pathognomonic of Marfan's syndrome. The complete triad of skeletal, ocular, and aortic abnormalities provides the most substantial basis for the diagnosis of Marfan's syndrome. Study of families confirms that incomplete forms of the syndrome (formes frustes) do occur.

The association of dislocated ocular lenses with brachymorphism is known as the Weill-Marchesani syndrome. The patient with this syndrome is short and has a round head and short, pudgy extremities. Two of the 33 affected members of the S. family are accepted as examples of the Weill-Marchesani syndrome. The author assumes that the morphologic differences between the Weill-Marchesani and the Marfan syndrome do not justify any genetic distinction between the 2 syndromes.

The incidences of the stigmata of Marfan's syndrome in the 17 affected members known to have been examined by physicians or optometrists were: dislocation of ocular lenses, 94%; dolichocephaly, 94%; arachnodactyly, 70%; clinical evidence of aortic disease, 15%. The incidences of these stigmata did not change appreciably from one generation to the next in the medically examined affected members of the 4th, 5th, and 6th generations. Affected male members now dead had a lower fertility rate (average, 0.4 child each) and less capacity to transmit the abnormal gene (average, 0.1 affected child each) than did affected female members (average, 4.7 children each; average, 2.3 affected children each). The average lifespan of 16 deceased affected members was 45 years. Cardiovascular diseases caused the deaths of at least 11 of 17 affected members; aortic disease accounted for at least 3 of the 11 deaths attributed to cardiovascular disease.

These observations support the conclusions that, in the S. family, Marfan's syndrome is transmitted by a single pleiotropic abnormal gene; expression of this gene results in an abiotrophy of the cardiovascular system. Prohibition of childbearing by affected women would be expected to reduce the number of affected persons in succeeding generations.

SURGERY

Open Heart Surgery at the San Juan City Hospital. F. L. Raffucci, J. F. Bernal, M. Blasini and others. Bol. Asoc. méd. Puerto Rico 51:347-353 (Oct.) 1959 (In English) [Santurce].

Three patients with cardiac symptoms were observed at the San Juan (Puerto Rico) City Hospital; the ages of the patients ranged from 16 to 47 years. Diagnosis of an interatrial septal defect was made from the results of clinical, electrocardiographic, and roentgenographic examinations and of cardiac fluoroscopy. Repair of the interatrial septal defect was carried out under direct vision of the defect, with the patient under moderate hypothermia, the temperatures at caval occlusion varying between 27 and 28 C (80.6 and 82.4 F). No complications occurred during the operation in the first and second patients. In the third patient, ventricular fibrillation developed immediately after the closure of the defect. Fibrillation was converted into normal sinus rhythm by application of cardiac massage. The immediate postoperative period was free from complications in the first and third patients. In the second patient, massive atelectasis of the left lung developed on the second day after operation; it did not improve with tracheal aspiration, but was controlled by tracheotomy. There were no deaths in this group. The patients were discharged between 30 and 34 days after operation. A follow-up for one year showed that they were asymptomatic. The authors conclude that moderate hypothermia is the easiest and safest procedure to be used in open-heart surgery for the repair of an interatrial septal defect.

A Clinicopathologic Review of 80 Cases of Struma Lymphomatosa. A. A. Stein. Surg. Gynec. & Obst. 109:544-548 (Nov.) 1959 [Chicago].

A review of 143 cases of diffuse chronic thyroiditis, in which operation was performed at the Albany (N. Y.) Hospital between 1937 and 1953, revealed 80 cases which presented the features of chronic lymphomatous thyroiditis, also known as struma lymphomatosa or Hashimoto's disease. The clinical records and the pathological materials were carefully studied. While the patients ranged in age from 10 to 70 years, the average age was 53.3 years. Only 6 of the 80 patients were men. In more than half of the patients goiter had existed for 5 years or more, and in many of them since childhood. New complaints—either onset of toxicity, glandular enlargement, pressure effects, or hypothyroid features noted in the preceding few weeks or months—induced many of the patients to request medical aid. Initially the thyroid increased in size and weight, but in the late stage it became small and sclerosed.

After subtotal resection, most patients had signs and symptoms of myxedema within a few weeks. These patients needed and received comparatively large doses (1 to 3 grains) of desiccated thyroid daily and showed no sensitivity to thyroid on initiation of therapy. Follow-up examination indicated the need for continuous medication. Except for the relief of pressure symptoms, subtotal resection of these glands, even if the diagnosis is delayed until surgical exploration, seems unnecessary. At the time of surgical exploration, the surgeon can usually make the correct gross diagnosis. Any surgical procedure only hastens the inevitable hypothyroidism. Morphologically, the thyroid was composed of 2 types of epithelial structures, microfollicles and macrofollicles. Each follicular variant had distinct patterns of hyperplasia and involution. The variation in number and functional activity of these 2 epithelial structures created graded differences in morphologic pattern. The variations in clinical features merely reflected the proportion and activity of these 2 structural units.

Experimental Evaluation of Systemic and Coronary Arterial Pressure Response Associated with Ligation of the Internal Mammary and Subclavian Arteries. R. J. Botham, G. G. Rowe and J. W. Gale. Am. Heart J. 58:719-725 (Nov.) 1959 [St. Louis].

The authors discuss data acquired in an experimental evaluation of the systemic and coronary arterial pressure response associated with ligation of the internal mammary arteries in dogs. These studies were undertaken in an attempt to establish whether internal mammary artery ligation is followed by a demonstrable rise in pressure in the proximal segment of the internal mammary artery, whether the associated rise in pressure, if it occurs, is transmitted into branch arteries, and, lastly, whether the rise in pressure is localized to the internal mammary-pericardiophrenic system. Healthy mongrel dogs, weighing 18 to 28 kg. (40 to 62 lb.), were used. Group 1 consisted of 10 dogs in which simultaneous pressure determinations were recorded from the internal mammary, subclavian, and femoral arteries. Pressures were first measured and recorded prior to, during, and subsequent to ligation of the left internal mammary artery. Pressures were then measured and recorded prior to, during, and subsequent to ligation of the left subclavian artery. Group 2 consisted of 5 dogs in which simultaneous pressures were recorded in the subclavian and left anterior descending coronary arteries prior to, during, and subsequent to ligation of the left internal mammary and subclavian arteries. Group 3 consisted of 5 dogs in which extrapleural bilateral internal mammary artery ligations were performed. Direct arterial punctures with no. 20 needles allowed simultaneous intra-arterial pressure determinations from the proximal and distal segments of the ligated arteries at periods of 2, 4, and 5 weeks after ligation of the arteries.

Ligation of the internal mammary artery in dogs was found to cause an associated consistent rise in pressure of a varying magnitude in the proximal segment. The rise in pressure in the proximal segment of the ligated artery was transmitted from the parent vessel to its branch segments. The evoked pressure response, however, was not localized to the internal mammary-pericardiophrenic system but was a simultaneous generalized response recorded in both the systemic and the coronary arterial system. The nature of the pressure response suggested that the generalized rise in the systemic and coronary arterial pressure after ligation of the systemic artery was due in part to neural and/or humoral factors.

Results and Evaluation of Subtotal Adrenalectomy in Patients with Hyperfunction—Cushing's Syndrome: Report on Six Cases. J. M. Bayer. Arch. klin. Chir. 291:531-561 (no. 6) 1959 (In German) [Berlin].

The author reports on a 49-year-old man and 5 women, between the ages of 20 and 43 years, with adrenal cortical hyperfunction (Cushing's syndrome), who were operated on at the surgical clinic of the University in Bonn, Germany. The duration of symptoms before the surgical intervention varied from 2 to 17 years. All the patients had blue-red moon face, buffalo hump, obesity of the trunk, and intumescent abdomen. There were eosinopenia and excretion of large amounts of steroid in the urine. All the patients had hypertension ranging from 130/80 to 230/125 mm. Hg. Two patients had a high degree of osteoporosis. All the patients had a marked tendency to infections. The women had disturbances of the sex cycle, and the man complained of complete loss of libido and of potency. One of the women had a depressive-paranoid psychosis, and 2 other women and the man were apathetic and depressed. The carbohydrate metabolism was disturbed in 4 women and in the man.

Surgical treatment consisted of resection of seven-eighths of the right adrenal gland and of two-thirds of the left adrenal gland in one woman who was the first to be operated on. In the other 5 patients, one adrenal gland was removed completely and four-fifths to seven-eighths of the other adrenal gland was removed. Thus, 90 to 94% of the total gland substance was removed. All operations were performed in 2 stages. The acute risk in the immediate postoperative period and the necessity of long-continued administration of cortisone to combat relative cortical insufficiency, depending on the adaptation to the excessive adrenal cortical hormone, have been emphasized. All 6 patients survived the operations and were followed up for periods ranging from 15 months to 6 years and 3 months. In the woman who was the first to be operated on, an incomplete remission was obtained because of the insufficient adrenal resection; after 15 months this patient's condition became gradually worse, particularly concerning hypertension, although a complete relapse did not occur. The other 5 patients who underwent subtotal adrenalectomy had a complete remission except for the hypertension in 2 patients and except for the osteoporosis. The blood pressure was restored to normal, or considerably improved, in 3 patients. The osteoporosis regressed, but was still notable. There were neither clinical nor biochemical indications of an actual or imminent recurrence. Two of these 5 patients are living without any substitution therapy; intramuscular exogenous corticotropin (ACTH) tests, however, showed that there was no return of function of their adrenal remainders. One patient required a small dose of cortisone daily. The remaining 2 patients had complete adrenal insufficiency; a salt-loss syndrome developed, which required the administration of a mineral corticoid preparation. In one of these patients work capacity was restored by substitution therapy, but within 16 months after the adrenalectomy the first manifestations of a pituitary tumor appeared. In the other 4 patients with subtotal adrenalectomy, the total results were highly satisfactory. Characteristic changes of the skin of the face and of the extremities, such as dryness, itching, and fine-lamellar scaling, occurred early after the operation in these patients, and are to be considered as definite signs of the success of the adrenalectomy. In one patient a preoperative glaucoma subsided after the operation.

The necessity for early diagnosis and early operation in patients with adrenal cortical hyperfunction is emphasized with respect to the insufficient effect on hypertension in the presence of secondary vascular lesions. The advantages and disadvantages of subtotal and total bilateral adrenalectomy are discussed. Franksson's method of autotransplantation of adrenals into the sartorius muscle, combined with total adrenalectomy, deserves a trial on a larger scale. Careful follow-up with respect to the formation of pituitary tumors after total adrenalectomy is imperative.

Primary Repair of Benign Strictures of the Bile Duct. R. B. Cattell and J. W. Braasch. Surg. Gynec. & Obst. 109:531-538 (Nov.) 1959 [Chicago].

From 1919 to May, 1959, 690 patients with benign biliary stricture have been treated at the Lahey Clinic with 1,006 operative procedures. From this series a group of 501 patients, first seen between the years 1940 and 1955 inclusive, has been selected for closer scrutiny, particularly as regards indications for operation and the results of primary stage repair. A total of 447 primary repairs of biliary stricture have been performed in this group of 501 patients, including 207 end-to-end anastomoses of the duct, 142 hepaticojejunostomies, 15 hepaticoduodenostomies, 46 plastic procedures, and 37 dilatations of ductal strictures.

The results 3 or more years after primary repair of biliary stricture are tabulated. The authors believe that strictures are likely to recur after this period of time. Of the patients reporting a satisfactory result 3 years after operation, only 4% subsequently noted return of symptoms of the disorder. The majority of the patients with satisfactory results have experienced no symptoms referable to the biliary tract. The others (5 to 10%) have only infrequent, mild symptoms of obstruction. The postoperative mortality rate ranged from 2 to 5%, and the satisfactory results at the end of 3 years ranged from 43 to 68% after the various methods of repair. The authors regard the end-to-end repair with anastomosis of the 2 ends of the bile duct as the procedure of choice for benign biliary stricture. This procedure should be accomplished over an inlying T tube, the vertical limb of which is brought out either above or below the anastomosis.

Partial Controlled Splenectomy: Preliminary Report on the First Three Cases. M. C. Christo. Hospital 56:645-650 (Oct.) 1959 (In Portuguese) [Rio de Janeiro].

The author presents a surgical technique for "partial controlled splenectomy," developed according to the concept of independent vascular areas in the spleen presented by Zappalá and Neder at the University of Minas Gerais, Brazil. The first 3 patients operated on by this technique were a 40-year-old man with a knife wound, a 6-year-old girl, and a 23-year-old man with a bullet wound. The choice of technique in all 3 cases was dictated by the nature of the wound, a thoracophrenolaparotomy at the left intercostal space being the adequate surgical approach. In each of the 3 patients the spleen had been perforated and bled profusely. The arterial branches in the wounded area were ligated, which caused immediate arrest of the hemorrhage. A dark, shrunken purple area could be seen at the lower splenic end, its aspect contrasting with the rest of the organ. The spleen was resected on both sides of the dark area (approximately 5 cm. on each side), and the whole lesion was removed with an incision perpendicular to the great axis of the organ. There was a mild hemorrhage from arterial branches, which was arrested by ligation. The gastric and pulmonary areas involved were repaired, and the wound was closed in planes. Two patients required pleural drainage.

In each of the 3 patients it was possible to observe the presence of a thin splenic arterial interzonal branch.

The author recommends that after the partial resection the bleeding surface of the remaining spleen be covered with Gelfoam and not with the epiploon. In the resection of intermediate areas the remaining portions may be united by separate stitches in the organ's capsule. The use of partial splenectomy is recommended not only for localized traumatic lesions of the spleen but also for any pathological process limited to a definite splenic "vascular area."

The Emergency Portacaval Shunt. G. E. Wantz and M. A. Payne. Surg. Gynec. & Obst. 109:549-554 (Nov.) 1959 [Chicago].

Whenever possible, the authors have treated bleeding esophagogastric varices by decompressing the portal bed with an end-to-side portacaval shunt as soon as the hemorrhage has been controlled by esophageal tamponade, and the patient's vital signs have been stabilized. They present an analysis of their experiences with this emergency portacaval shunt in 24 patients treated at the New York Hospital–Cornell Medical Center, since 1950. The series included 7 women and 17 men, whose ages ranged from 16 to 70 years and averaged 47.7 years. Fifteen patients had alcoholic cirrhosis, and one of these had a hepatoma. Four patients had postnecrotic cirrhosis, and one of these also had hepatic endophlebitis. Four patients had primary biliary cirrhosis, and in one of these it was associated with hepatoma. There was one patient with a proliferative endophlebitis of the hepatic veins. Both instances of hepatic endophlebitis and both instances of hepatoma went unrecognized until postmortem examination. None of the patients were in hepatic coma at the time of operation.

Three groups of patients were differentiated according to the degree of hepatic damage. Group A patients had mild hepatic disease with a bilirubin content of less than 2 mg. and an albumin content of more than 3.5 Gm. per 100 cc.; they had never been in a coma, and did not exhibit ascites or muscle wasting. Group B patients had moderate hepatic damage when icterus was present, but the bilirubin content was less than 3 mg. and the albumin was usually between 3 and 3.5 Gm. per 100 cc. These patients had never had more than moderate muscle wasting; they had never been in coma, and when ascites was present, it was transient and easily controlled. Group C patients had advanced hepatic disease and jaundice, and their serum albumin level was usually below 3 Gm. per 100 cc. They had frank muscle wasting and had been in coma; ascites generally existed and was difficult to control.

Review of the cases revealed that the over-all condition of the patient, as judged by muscle wasting, coma, and jaundice, constituted the significant prognostic feature, since 6 of 8 patients with marked atrophy of the muscles died and 5 of the 8 patients who had been in a coma before the operation also died. In answer to the question as to why poor-risk patients were subjected to an operation of the magnitude of portacaval shunt, the authors point out that in 11 patients shunts were used because bleeding recurred immediately or within 1 to 3 days upon deflation of the esophageal balloon. The fact that patients with cirrhosis deteriorate with recurrent bleeding led them to attempt early portal decompression in an effort to salvage more of them. Thus far, the authors have performed an end-to-side portacaval shunt on 7 patients without waiting to see if bleeding would recur upon discontinuing pneumatic tamponade, but whereas the 5 patients with mild or moderate cirrhosis recovered, the 2 with advanced cirrhosis died. Of 15 poor-risk patients with demonstrably unrelenting hemorrhage, 6 survived to lead normal lives. Although the operative mortality is bound to be high in these patients, without surgical intervention death seems inevitable.

The authors conclude that portacaval shunt need not be delayed in patients who have been in a steady state of comparatively good health prior to bleeding from esophagogastric varices. However, patients whose health has progressively deteriorated before hemorrhage and in whom the bleeding represents additional evidence of hepatic decompensation should be given a trial of balloon tamponade. Provided that the patient is not moribund or preterminal, portacaval shunt offers the only certain method of controlling massive hemorrhage which continues or recurs despite correct nonoperative treatment. Operation is probably contraindicated in patients with marked jaundice or with a serum bilirubin value exceeding 4 mg. per 100 cc. associated with portal cirrhosis.

The Clinical Behavior and Management of Primary Malignant Lymphoma of the Stomach. G. McNeer and J. W. Berg. Surgery 46:829-840 (Nov.) 1959 [St. Louis].

Thirty-six patients with an apparent primary lesion in the stomach, and with metastases confined to the perigastric area, were observed at the Memorial Center for Cancer and Allied Diseases in New York during 1935-1956. This series represented 2.2% of all malignant tumors of the stomach seen at the center during that period. The practical criterion established in this study for confirmation of the primary character of the tumor was applicability of standard gastrectomy as a therapeutic procedure. There were 22 men and 14 women in this series. Only 3 patients were under 40 years of age; the great majority (24) were in the 50-70 age group. The average duration of symptoms prior to the start of a definitive treatment was 8 months, the longest duration being 3 years, and the shortest 1 day. The commonest clinical picture was suggestive of peptic ulcer. In 9 patients there was an acute loss of weight, which the authors consider characteristic of primary gastric lymphoma. In 2 patients there were palpable abdominal masses.

The 36 patients underwent surgery. Five of them had only laparotomy because of the advanced stage of their disease. In one patient, whose massive lesion of the cardia had been diagnosed as lymphosarcoma on biopsy, the tumor resolved completely under x-ray therapy, and the man was still free from disease 19 years later. Seventeen patients underwent subtotal gastrectomy, and 14 total gastrectomy. Postoperative radiation was administered unsystematically, either with the radio cobalt unit or x-ray voltages of one million or more to give the tumor a dose of 3,000 to 4,000 r. There were 1 operative and 3 postoperative deaths; 5 patients died within 3 years. Twenty patients were followed up in a 5-year survey. There were 7 survivors, 5 of whom had received the combined gastrectomy-radiation treatment. Histologically, 3 types of tumor were distinguished—purely lymphocytic tumor, reticulum-cell tumor, and an intermediate group. At a 3-year follow-up the survivors were 4 patients with lymphocytic tumor, 2 of 8 patients with the intermediate type, and 3 of 6 with reticulum-cell lymphoma. The authors conclude that radical surgery plus radiation therapy is the most effective form of treatment, and that the only clinically significant separation of the operable lymphomas by cell type lies in the segregation of the purely lymphocytic lymphoma from the tumors with any less differentiated components.

Cancer in Ulcerative Colitis. G. Slaney and B. N. Brooke. Lancet 2:694-698 (Oct. 31) 1959 [London].

In the past decade the development of surgical methods in the treatment of ulcerative colitis has brought increasing awareness of the problem of carcinomatous change. Reports from the literature indicate that cancer of the large intestine is much commoner in patients with ulcerative colitis than in persons without it. The incidence of cancer in medically treated patients with ulcerative colitis has been found to be between 3 and 4%, and in surgically treated patients to be twice as high; it has been known to reach 30% when ulcerative colitis had been present for 10 years or more.

Data are presented on 18 patients in whom carcinoma arose subsequent to ulcerative colitis. Fifteen of the 18 patients belonged to a series of 222 patients with ulcerative colitis, who had been referred to the authors for surgical treatment. The over-all incidence of carcinomatous change was 6.7%, and rose to 17% in those with ulcerative colitis of 10 or more years' duration. An analysis of this and other series suggests that the 5-year survival rate in cases of carcinoma complicating ulcerative colitis is no higher than 18.6%. The average age at which carcinoma develops is 42 years in those with ulcerative colitis, compared with 63 years in previously healthy persons. Carcinoma may develop after a quiescent or healing phase. The lesion can be difficult to detect clinically, radiologically, and on naked-eye inspection of the intestine after removal. Simple deflection of the fecal stream by ileostomy does not protect the intestine from malignant change, which can arise both in retained and in defunctioned large intestine and in a functioning rectum after ileoproctostomy.

Interruption of the Pituitary Stalk in the Patient with Mammary Cancer. G. Ehni and N. E. Eckles. J. Neurosurg. 16:628-652 (Nov.) 1959 [Chicago].

The authors report on 17 women, between the ages of 26 and 58 years, with metastasized cancer of the breast, who were subjected to section of the pituitary stalk, followed by implantation of a mechanical barrier to regeneration of the hypophysial portal vessels, at the Anderson Hospital in Houston, Texas. There were 2 operative deaths. The other patients survived for periods ranging from 2 to 22 months. Interruption of the pituitary stalk produced regression of the widespread breast cancer in 5 patients who showed improvement by gain in weight, improved erythropoiesis, diminished calcium excretion, roentgenographically observable osteoblastic change, and, in some instances, resumption of normal trabecular pattern in bone lesions. In 4 of these 5 patients lactation was discovered 1 to 10 months after the operation. Lactogenic hormone, seemingly elaborated by the surviving pars distalis, unaided by ovaries or adrenals, produced and maintained lactation in these patients. It is believed that impairment of secretion of the milk-ejection factor deriving from the posterior lobe accounted for failure of lactating women to become aware of lactation spontaneously.

Laboratory findings during the postoperative survival period revealed that the output of adrenocorticotropic hormone was greatly depressed after interruption of the stalk. The thyroid-stimulating function of the pituitary gland was greatly reduced in most of the patients, but this reduction seems not to be as invariable or as immediate as it has been reported to be after efficient hypophysectomy. The anti-insulin effect of the normally functioning anterior lobe was reduced strikingly in some patients but was reduced only moderately in others. Division of the pituitary stalk produced polyuria in all but one surviving patient. It did not appear that this development was conditional on persisting function of the anterior lobe or on substitution therapy given for deficiency of the anterior lobe. Judging from the effects on menstruation and on the ovaries, uterus, and vagina of one long-term survivor, interruption of the stalk abolishes gonadal-stimulating and genital-stimulating activity of the pituitary gland.

Autopsy findings revealed that section of the pituitary stalk produced infarction in the anterior lobe of the pituitary, which corresponded with the pattern of infarction in the medial portion of the pars distalis with extensions laterally, which had been observed by other workers in rats. Histological examination of the viable-appearing cells by a variety of techniques, calculated to reveal specific losses of cells or cytological abnormalities, failed to show them, and no difference is believed to exist between the parts of the anterior lobe which survived interruption of the stalk and the normal. The cells that survive may amount to one-fourth of the preoperative volume of the anterior lobe. The isolated surviving cells of the anterior lobe probably behave in a fashion identical with pituitary isografts.

The reported data showed the authors' hypothesis, which maintained that interruption of the pituitary stalk is the physiological equivalent of total hypophysectomy, to be invalid. While the effects on the gonads and the adrenals seem substantially the same, the effects on the thyroid and on carbohydrate metabolism may be milder or less consistent. The greatest difference between the 2 interferences with function of the anterior lobe lies in the lactational effect of interruption of the stalk. Though the authors' experience shows a positive association between lactation and regression of the tumor, it cannot be asserted that lactation so produced is of benefit in breast cancer. Though this series is too small to support a conclusion comparing the efficacy of interruption of the stalk with hypophysectomy in the treatment of breast cancer, the anticancer effects of the two appear to be similar. The observed association between lactation and regression of the tumor deserves further study.

Hepatic Artery Aneurysm: Report of a Case Treated by Excision. J. G. Jontz. Surgery 46:896-901 (Nov.) 1959 [St. Louis].

The author reports a case, which he believes to be the 6th, of total excision of an aneurysm of the hepatic artery. The patient, a 67-year-old man, was hospitalized at the Medical Center of Indiana University, in Indianapolis, because of a pulsating mass in his lower abdomen which had been present for 5 years. This mass had been increasing in size, and the patient had been suffering from epigastric discomfort which seemed to be aggravated by the ingestion of fatty foods. Physical examination showed a blood pressure of 190/90, pulsus alternans, and a grade 2 systolic murmur at the apex. There was a mass, about 5 by 10 cm., in the middle of the lower abdomen, tender to palpation, with intrinsic pulsation and a systolic bruit. The electrocardiogram showed a complete left bundle-branch block, premature atrial beats from different foci, and short runs of tachycardia. The roentgenologic examination revealed calcium in an abdominal aortic aneurysm and in what was interpreted as a possible splenic artery aneurysm.

The patient was placed on digitalis therapy, and his cardiac rhythm difficulties improved. At operation, an abdominal aortic aneurysm was found, measuring 4 by 4 by 6 cm. This aneurysm was excised, and a straight, stretch-weave Dacron graft was interpolated between the transected ends of the aorta. An aneurysm of the hepatic artery arose from the common hepatic artery and ended at the gastroduodenal branch. The hepatic artery was occluded proximally and distally with noncrushing vascular clamps, while the gastroduodenal, right gastric, right and left hepatic arteries maintained pulsatile blood flow. The aneurysm was excised, and the transected ends of the hepatic artery were sutured with a 5-0 arterial suture. Antibiotic postoperative therapy was instituted. The patient made an uneventful recovery and remained in good health 9 months after his discharge from the hospital.

A 26 Year Experience in the Surgical Treatment of 5,037 Patients with Nonmalignant Biliary Tract Disease. F. Glenn. Surg. Gynec. & Obst. 109:591-606 (Nov.) 1959 [Chicago].

Since 1932 a careful account has been kept of patients with biliary tract disease, who have been cared for in the surgical pavilions of the New York Hospital-Cornell Medical Center. During this period detailed records have been maintained and frequently reviewed. Concomitantly, numerous studies upon selected groups of patients have been made. By 1958 a 26-year period had elapsed, during which 5,037 patients had been treated surgically for nonmalignant biliary tract disease. The author has reviewed clinical experiences in conjunction with follow-up evaluation of patients who have been observed for long periods. He has also investigated the present policies and practices in the management of patients with biliary tract disease.

The author found that there has been a wider acceptance of surgical therapy for this malady. Contributing to this trend has been a reduction in the morbidity of complications and in the mortality rate. Surgery is accomplished with greater ease as well as with increased safety. It is contended that this trend will continue as the time interval between the establishment of diagnosis and operation is further reduced. Evaluation of patients with anticipation of possible complications, resulting in better preoperative preparation and meticulous attention to the technical steps involved, should improve the results in the future. The difference in the mortality rate of 0.5% for 2,712 patients under 50 years of age and 3.2% for 2,325 patients 50 years of age and older, treated surgically for nonmalignant disease of the biliary tract, emphasizes the importance of early diagnosis and early operation.

Experience with Hypophysectomy in Inoperable Cancer of the Breast. E. Pardal, A. Belou and A. R. Walder. Prensa méd. argent. 46:1041-1045 (April 24) 1959 (In Spanish) [Buenos Aires].

Ten women, between 49 and 75 years of age, with metastasized cancer of the breast, underwent hypophysectomy as a palliative treatment. All 10 patients had been operated on before, 9 having undergone mastectomy and one being subjected to resection of the mammary nodule. The hypophysectomy was performed through a transseptosphenoidal approach and by curettage. Premedication consisted of 100 mg. of cortisone given every 12 hours over a period of 48 hours immediately preceding the operation. The postoperative period was complicated in one patient by diabetes insipidus, which developed in consequence of the high resection of the hypophysial stem; in another patient there developed a fistula discharging cerebrospinal fluid, which subsequently led to meningitis and death.

All 10 patients experienced relief from pain and a satisfactory hormonal balance immediately after the hypophysectomy. In only one patient was this relief temporary. Seven patients were living at the time this article was written. The survival rate varied from 2 to 11 months. Six of the surviving patients were in good general condition and free from symptoms. The 7th survivor was the patient who suffered a relapse of pain. The authors believe that the effects of hypophysectomy are manifest within a few hours after the operation, bringing about a feeling of well-being and relief from the symptoms. In the great majority of patients the tumors decrease in size, the local trophism is improved, the osseous metastases are calcified, and the pathological fractures are consolidated.

Elective Cardiac Arrest by Anoxia During Extracorporeal Circulation. G. Dubourg, F. Fontan, D. Cottin and others. Semaine hôp. Paris 35:3081-3085 (Nov. 18) 1959 (In French) [Paris].

The authors performed a series of experimental studies on dogs in order to compare in open-heart surgery 2 methods of elective cardiac arrest, that is, by the injection of potassium citrate and by anoxia during extracorporeal circulation. The latter method offered by its innocuousness, its effectiveness, and the simplicity of its technique considerable advantages over elective cardiac arrest by potassium citrate. Complete cardiac arrest was less rapidly induced by anoxia than by the injection of potassium citrate, requiring from 8 to 10 minutes; this delay, however, proved to be an advantage because it enabled the surgeon to operate on a completely dry and flaccid heart. Elective cardiac arrest by anoxia was used during open cardiotomy in 15 patients with various heart diseases, their ages ranging from 5 to 30 years. The heart-lung apparatus of Senning was used in all the patients. Of the 15 patients, 12 were cured; the 3 deaths could not be ascribed to the effect of anoxia. The greatest advantage of this method lies in the fact that the conductive bundles can be controlled at will and the arrest of coronary circulation can be repeated as many times as necessary, whereas the injection of potassium citrate cannot be given repeatedly. After removal of the clamps, normal heart rhythm was resumed much more rapidly than after cardiac arrest by potassium citrate. The authors emphasize that, in their opinion, cardiac arrest by anoxia is the method of choice in open operations for the correction of congenital heart disease.

Embolectomy in Protracted Fatal Pulmonary Embolism. R. Nissen. Schweiz. med. Wchnschr. 89:1169-1172 (Nov. 7) 1959 (In German) [Basel, Switzerland].

Of the 19 patients with pulmonary embolism whose lives were saved by embolectomy, 11 were operated on during the 16 years between 1924 and 1940, and only 8 during the last 18 years from 1941 to 1959. In view of the decisive advancement in cardiovascular surgery during the recent years, the author feels that this decrease in the performance of Trendelenburg's embolectomy is somewhat surprising, the more so since some of the advances in cardiovascular surgery might prove helpful in the Trendelenburg embolectomy. He points out that the majority of massive pulmonary embolisms are immediately fatal and that it is inadvisable to perform embolectomy practically after death, in the hope that cardiac massage will revive the patient, for although heart action may be restored, the brain will have suffered irreparable damage. For these reasons embolectomy should be attempted only in those whose heart is still functioning after all preparations for the operation have been completed, including exposure of the pulmonary artery. Even in hospitals that are fully equipped for emergency embolectomy, from 15 to 30 minutes will be necessary for preparation. It will be found that in many patients immediate embolectomy will no longer be necessary, because there has been spontaneous recovery from the embolism.

At the author's clinic it is the practice to prepare for embolectomy patients in whom the symptomatology indicates massive pulmonary embolism, and to have the surgical staff and sterile instrumentarium in readiness, while the patient's blood pressure, respiration, degree of dyspnea, and inflow stasis are kept under constant watch. The data obtained in this manner are just as informative as continuous electrocardiographic recordings. Under such conditions, the author performed the Trendelenburg embolectomy on 2 patients with what has been designated "slowly fatal acute cor pulmonale." He reports on a 73-year-old woman on whom a successful embolectomy was performed 24 hours after the first signs of embolism. The 24-hour delay makes the case noteworthy, since among the 19 successful operations for pulmonary embolism recorded in the literature there were only 2 others with similar intervals between onset and operation, 18 hours in one case and 40 in the other.

The Management of the Ruptured Aortic Aneurysm. J. Storer and R. C. Smith. A. M. A. Arch. Surg. 79:711-714 (Nov.) 1959 [Chicago].

Aneurysm of the abdominal aorta can be detected by palpation. When the patient is lying on his back, a pulsating mass can be felt even in the obese patient. A high index of suspicion on the part of the surgeon is important. Backache is an important symptom, and many aneurysms are detected by radiologists during "back studies." Aneurysms usually rupture within a few years. Since the aorta is retroperitoneal, the ruptured aneurysm may be contained by the peritoneum for a time, but when the enlarging hematoma ruptures the peritoneum, death threatens. The initial abdominal pain may be so intense as to cause syncope. Irritation of the sigmoid colon frequently causes diarrhea. The blood may dissect along the retroperitoneal tissues and present in the inguinal canals, leading to a mistaken diagnosis of incarcerated inguinal hernia.

As soon as the diagnosis is made, a blood count, urinalysis, blood typing, and cross matching are the only laboratory procedures requested. The patient is taken to the operating room immediately. Two "cut-downs" are done, and blood transfusion is started. In their first operations for ruptured aneurysms, the authors paid little attention to the anesthetic management, but now they use neuromuscular blocking agents prior to induction of anesthesia. The patient is completely paralyzed by succinylcholine (Anectine) chloride. Endotracheal intubation is then accomplished, and the patient is anesthetized.

The abdomen and left chest are draped, and a lower left rectus incision is made. A submammary incision is made in the left side of the chest. The pleura is entered, the aorta is isolated just above the diaphragm and a Satinsky clamp placed around it, but its jaws are not closed. The abdominal incision is then lengthened to the pubis, the viscera packed off, and dissection begun. The aorta is isolated above the aneurysm, which is usually below the renal arteries. In what the authors refer to as the "friendly space," where the vena cava and the aorta are usually not adherent, blunt dissection with the index finger will enable the surgeon to encircle the vessel in a few minutes. The Satinsky clamp is removed from the thoracic aorta and placed across the abdominal aorta at the point of dissection. Again, the jaws are left open. Removal of the aneurysm is carried out, and aortic continuity is reestablished by the insertion of a preclotted elasticized Dacron graft. The jaws of the Satinsky clamp are closed only if bleeding seriously interferes with manipulation.

The authors have seen no serious impairment of renal or hepatic function by clamping the aorta for 10 minutes. They describe 3 illustrating case histories. They conclude that excision and grafting are the ideal treatment of an arteriosclerotic aneurysm of the abdominal aorta. The aneurysm should be thought of as a malignant lesion. One should not postpone surgery any more than if one were dealing with a carcinoma of the large intestine. The diagnosis of aortic aneurysm must be considered in the presence of the signs of the "acute abdomen" in patients past the 4th decade.

The Surgical Management of Functional Adrenal Hypercorticism. R. C. Overton, J. W. Overstreet and R. V. Ford. A. M. A. Arch. Surg. 79:791-798 (Nov.) 1959 [Chicago].

The improvement of laboratory techniques for diagnosis of abnormal adrenal states has made it possible to detect patients in an earlier phase of hyperadrenocorticism than that which is usually referred to as Cushing's syndrome. The authors present observations on 16 of these patients who were subjected to total bilateral adrenalectomy. They believe that hyperadrenocorticism is initially a cyclical disease, which is generally progressive. Since there is no chemotherapeutic agent that will inhibit hypercorticism (without prohibitive toxicity), the authors regard total adrenalectomy as not too drastic a procedure in view of the prognosis of untreated hypercorticism. All except 1 of the 16 patients were women of an average age of 35 years (range from 18 to 53 years). Age greater than 55 years and renal impairment, indicated by a blood urea nitrogen concentration of greater than 30 mg. per 100 cc., were accepted as contraindications to surgical removal of the adrenals. Congestive heart failure, however, was not considered as a contraindication, since 3 of 16 patients were bedridden from cardiac failure for one year or more prior to adrenalectomy.

No preoperative priming with supplemental steroid is instituted, but at the beginning of the procedure, through a separate intravenous infusion, administration of 100 mg. of hydrocortisone, in 1,000 cc. of 5% dextrose in isotonic sodium chloride solution, is started at a slow rate. After both adrenals have been removed, the patient usually receives approximately 30 to 40 mg. of hydrocortisone. Repeated observations of vital signs and hourly urinary output provide the indexes for supportive medications and immediate postoperative management. Vasopressor agents are not necessary. In spite of the ablation of the adrenal medulla, these patients maintain an adequate blood pressure if hydrocortisone and moderate amounts of salt are administered. During the first 24 hours the average hydrocortisone requirement has been 200 mg. administered intravenously by constant slow infusion. Occasionally, more than 9 Gm. of sodium chloride is necessary, particularly if the patient has been on a diuretic regimen. On the first postoperative day intravenous administration of hydrocortisone is continued in a decreased amount, and by the second postoperative day it is supplemented by orally administered hydrocortisone. With the transabdominal approach the patients have much less ileus than with the flank or retroperitoneal approach, permitting the rapid resumption of oral feedings and medication. The orally administered doses of hydrocortisone can be reduced rapidly to from 30 to 40 mg. daily in divided doses.

In spite of the fact that many of the 16 patients had serious hypertensive cardiovascular problems before operation, there were no deaths. The patients have since been followed for from 3 to 18 months, and it is evident that they have been benefited. They were treated at a stage in which their disease might be considered to be functional and not a fully developed Cushing's syndrome.

Glomus Tumor of the Leg: A Case Report. W. E. Hess. Rocky Mountain M. J. 56:51-52 (Nov.) 1959 [Denver].

Glomus tumor, also masquerading under such names as angiosarcoma, perithelioma, painful subcutaneous nodule, glomangioma, sugungual tumor, hemangiopericytoma, and angioneuromyoma, is a relatively rare condition even when found in its usual subungual location. The patient presented was a 52-year-old painter who complained of pain in the left knee of over one year's duration. He described the pain as stinging and burning and stated that even slight bumps and pressure of bed covers aggravated it. He had given up his job as a painter because bumping his knee on the rung of a ladder caused severe pain. The patient's history revealed that he had undergone excision of a torn medial meniscus in the same knee in 1929, following a twisting injury one year previously. Now there was a palpable, slightly mounded area over the anteromedial proximal tibial region on the left, about the size of a 50-cent piece. This area was exquisitely tender to pressure with the tip of a lead pencil directly over the center of the enlargement. The tenderness seemed to be in the skin, since raising the skin and displacing it to one side revealed no deep tenderness. There was a very slight bluish stain, visible only in bright light. Roentgenologic examination revealed a small spur on the patella. The clinical impression was possible glomus tumor. The lesion was excised.

The pathological specimen consisted of an elliptical wedge of skin. Subcutaneously, in the central portion of this wedge of skin, there was a small pink mass of tissue, 3 mm. in diameter. Microscopic examination revealed a well-circumscribed glomangioma. There was no evidence of malignancy. The patient had an uneventful convalescence; he is now free from pain and has been able to resume his work as a painter. The author's search of the literature revealed few reports on glomus tumors in the region of the knee joint.

Treatment of Malignant Pelvic Tumors by Extracorporeal Perfusion with Chemotherapeutic Agents. W. G. Austen, A. P. Monaco, G. S. Richardson and others. New England J. Med. 261:1037-1045 (Nov. 19) 1959 [Boston].

The toxicity of nitrogen mustards and allied compounds to the normal tissues of the gastrointestinal tract and of the hematopoietic system has limited their systemic administration. Direct intra-arterial administration of nitrogen mustard produces high local tumorocidal levels but does not entirely eliminate systemic toxicity. By isolating the circulation of a region bearing a tumor and perfusing it by a method utilizing an extracorporeal circuit, Creech and his associates achieved the twofold advantage of minimizing systemic toxicity and bringing high levels of alkylating agent to the tumor. An oxygenator was incorporated into the perfusion circuit because radiomimetic drugs are presumably more effective with high tissue oxygen tensions. In another communication, the application of regional perfusion of the lower extremity is described, while this paper is concerned with perfusion of the pelvis.

Vascular isolation of the pelvis is achieved by occlusion of the aorta and vena cava by suitable noncrushing vascular clamps and of the femoral vessels in both lower extremities by pneumatic cuffs inflated around the upper thighs. The technique of pelvic perfusion is described, and illustrative case histories are presented. Regression was achieved in 4 of 7 patients with pelvic cancer. Perfusing the pelvis with the patient's own blood, maintained at physiological temperature and pH, will avoid peritoneal reactions associated with the use of bank blood. The importance of monitoring pelvic perfusion pressure and systemic pressure is emphasized. Maintenance of the perfusion pressure at a lower level than the systemic pressure minimizes the loss of drug to the general circulation. The extent of mixing of the perfusate with the general circulation in pelvic perfusion is variable and not accurately predictable. Monitoring the rate of mixing of the 2 circulations during perfusion affords the best means of administering the maximal amount of agent with the minimal risk of systemic toxicity.

In the usual pelvic perfusion, the rate of mixing is approximately 1.5% per minute. Under such circumstances high doses of nitrogen mustard (1.0 mg. per kilogram of body weight) may be given safely. Obstruction of pelvic veins by tumor results in increased collateral blood flow. This is associated with a mixing rate of approximately 3% per minute and requires reduction of the dosage of nitrogen mustard to 0.8 mg. per kilogram of body weight. When occlusion of the major vessels is not complete or cannot be attempted, the drug is lost to the general circulation at a rate of approximately 4% per minute, and the permissible dose is 0.4 to 0.5 mg. per kilogram of body weight. Systemic toxicity is also dependent upon the duration of action of the drug. With the same rate of loss of perfusate to the general circulation, a short-acting drug is better tolerated than a longer-acting agent.

The employment of combinations of drugs with similar effects on tumors and different systemic toxicities may produce more damage to the tumor without increasing the hazard to the patient. It is possible that pelvic perfusion with nitrogen mustard compounds can be combined with radiation therapy for increased effectiveness. Perfusion with chemotherapeutic agents is particularly applicable to pelvic cancer, since tumors of this area frequently cause morbidity and mortality by local encroachment rather than by distant metastases. Control of local disease may result in prolonged survival.

Treatment of Kaposi's Sarcoma of the Lower Extremity by Extracorporeal Perfusion with Chemotherapeutic Agents. A. P. Monaco and W. G. Austen. New England J. Med. 261:1045-1052 (Nov. 19) 1959 [Boston].

Kaposi's sarcoma, or idiopathic multiple hemorrhagic sarcoma, is progressive, and it exhibits a wide range of clinical and histological variations. The initial lesion is most often found on the hands and feet, and it takes the form of a reddened, well-demarcated, insensitive macule that slowly increases in size. Histologically, the appearance is one of inflammation with dilatation of dermal vessels and round-cell infiltration. As the early macule enlarges and becomes elevated, the color darkens to bluish red with hemangiomatous characteristics. Microscopically, the features of a granulomatous reaction are apparent, for edema, hemorrhage, and connective-tissue proliferation are present. A widely accepted view is that the disease is a benign angiomatosis, arising from embryonal vascular cells at multicentric foci. Others belive that it is a true sarcoma and that secondary lesions are metastatic. A third concept holds that Kaposi's sarcoma is a disease of the reticuloendothelial system related to the lymphoma group, and its simultaneous occurrence in patients with Hodgkin's disease and related disorders supports this theory.

The authors discuss the therapy of Kaposi's sarcoma of the lower extremity on the basis of the histories of 2 patients in whom they employed regional perfusion with nitrogen mustard by means of extracorporeal circulation. They describe several types of lower extremity perfusion in which vascular isolation is complete enough, so that the limiting factor to the permissible dose of the chemotherapeutic agent is the tolerance of normal local tissue rather than systemic toxicity. In the adductor-canal perfusion 0.6 mg. per kilogram of body weight is employed, whereas 0.8 to 1.0 mg. per kilogram of body weight is well tolerated in the common femoral and external iliac perfusion. Extremes of perfusion pressure and flow must be avoided, and the patient's own blood, maintained at physiological temperature and pH, must be used to minimize limb edema and tissue swelling.

The case of the first patient, a 79-year-old man, illustrates 2 important aspects of Kaposi's sarcoma: the poor prognosis for a continued remission with radiation therapy once multiple tumors appear in the swollen, edematous extremity, and the complications of radiation therapy in the form of skin breakdown and indolent ulceration. Dye studies revealed essentially total isolation of the perfused extremity with only a 2% loss in 40 minutes and no evidence of systemic toxicity. Perfusion therapy achieved a gratifying and rapid remission in this patient without skin breakdown or other local sequelae. In the second patient, a 65-year-old man, perfusion therapy likewise achieved a gratifying and rapid remission without untoward sequelae. Both of these patients had previously received maximal tolerable doses of local roentgen irradiation. The authors suggest that the perfusion technique may permit previously heavily irradiated tissue to receive effective doses of nitrogen mustard and other radiomimetic agents without dangerous ill-effects.

The Prevention of Primary Postoperative Thrombosis: A Reliable Capillary Tube Clotting Time Method. H. F. McNickle. A. M. A. Arch. Surg. 79:775-784 (Nov.) 1959 [Chicago].

The author performed many hundreds of capillary tube clotting time estimations, for which homemade glass capillary tubes were used. Gradually, by trial and error, he found ways to eliminate some of the variables in the test. Unexpectedly, one of the most important variables was found to be in the capillary tubes themselves. This led to a study of the behavior of homemade capillary tubes when used to test the clotting time of normal blood at body temperature, and to the observation that freshly drawn capillary tubes give short and erratic clotting times, but that tubes from the same batch, after being allowed to age for some months, give very uniform and dependable clotting times, and continue to do so indefinitely. The next step was to use these reliable capillary tubes on patients undergoing major surgery in an effort to predict and forestall primary postoperative thrombosis and embolism. Such an investigation was begun in 1948 and is still continuing.

All batches of tubes were allowed to age naturally until they gave a clotting time of 7 minutes or longer when used on normal patients. The minimum aging time was at least 9 months when tubes were stored in a clear glass box standing on the desk in diffuse daylight. If the tubes remained on the desk after this, the aging process still continued but at a very reduced rate. The author found the capillary tube method reliable and feels that the failure of others to produce comparable results probably lies less in errors of technique than in a failure to appreciate the importance of aging the capillary tubes. It is a mistake to assume that all capillary tubes are identical in their effect on blood coagulation. The following are some advantages of the capillary tube test: 1. The capillary tube is a self-filling expendable container which holds a small sample of blood virtually out of contact with the air. 2. The tubes are clean, since a fresh one has to be used for each test. 3. No venipuncture is required. 4. The equipment is simple, and the test can be done quickly anywhere.

Postoperative clotting time estimations were planned to sort out those patients whose clotting mechanism became unstable in the early postoperative period. It was felt that, if the clotting mechanism had not been upset by the middle of the first week after operation, it was unlikely to become unstable thereafter, unless there were some complicating factor, such as dehydration, sepsis, or an intercurrent infection. Accordingly, the clotting time was studied routinely on the second and again on the third postoperative day. The test was made on 635 patients subjected to major surgery. Prophylactic anticoagulant treatment was given when the postoperative clotting time fell to half, or close to half, of the normal figure, as it did in 8 out of a total of 635 patients (1.3%). Heparin was the only anticoagulant used. It was given in frequent small doses by the subcutaneous route. The duration of treatment (from 2 to 10 days in this series; average, 5 days) was governed entirely by the duration of the patient's heparin resistance or tolerance. There has been no case, or suspicion of a case, of primary postoperative thrombosis since this investigation began 10 years ago.

NEUROLOGY & PSYCHIATRY

The Results of Injecting Hot Water into the Gasserian Ganglion for the Relief of Tic Douloureux.

R. Jaeger. J. Neurosurg. 16:655-663 (Nov.) 1959 [Chicago].

The author reports on 185 patients with paroxysmal trigeminal neuralgia (tic douloureux), who were treated by injecting hot water into the gasserian ganglion at the Jefferson Medical College Hospital in Philadelphia between 1953 and 1958. Relief from the paroxysmal tic pain has been complete in all but 7 patients. Five of these were among the first 30 patients, and they were relieved by operation. It is probable that at least 3 of these, if not all of them, could now be relieved by injection. There has been no operation for relief of the pain in the last 155 patients treated by injection Paralysis of the motor nerve to the muscles of mastication occurred in most, but not all, of the patients; complete regeneration of the motor nerve occurred within 3 or 4 months. There occurred suspected or slight temporary irritation of the cornea. Permanent slightly diminished vision was caused by clouding of the cornea in 2 patients. Slight paresis of the extraocular nerves occurred in 8 patients, but complete recovery always occurred in less than 5 months. Herpes occurred in more than 50% of the patients, usually on the labial mucosa at the corner of the mouth. It appeared 3 days after the injection and disappeared within 3 weeks. Some patients of advanced age or with an anxious, tense personality complained of numbness, stiffness, itching, burning, and crawling sensations over the anesthetized area. Injection of hot water into the gasserian ganglion has accomplished everything that the subtemporal or posterior fossa surgical approaches to the gasserian ganglion or its roots have, and without mortality, facial paralysis, and other complications common to major intracranial operation for tic douloureux.

A Follow-up of Head-Injured Men of World War II.

A. E. Walker and S. Jablon. J. Neurosurg. 16:600-610 (Nov.) 1959 [Chicago].

The authors report on 739 men who had sustained head injuries in World War II and who were followed up in 4 neurological centers in Baltimore, New York, Boston, and Long Beach, Calif., 6 to 9 years after injury. Mental disturbances in the form of impaired judgment, mentation, memory, and alterations in personality could be correlated with all factors related to severity of injury, but not with location of injury. Aphasia was present predominantly when the lesion in right-handed patients was in the left hemisphere, although 21% of such patients had major wounding on the right side. However, among the 47 left-handed patients who sustained head wounds, aphasia was associated only with left-sided lesions. Disturbances of the motor and sensory systems, commonly associated, tended to improve. Headache, usually associated with other post-traumatic symptoms, present in 82% of the men, did not correlate with the severity of injury, but bore a much closer relationship to the "neurotic" type of personality and subnormal intelligence. Some form of paroxysmal epileptic disorder occurred in 28% of the patients in this series, but only 22.9% had more than one definite attack. There was a distinct tendency for the prognosis to be favorable in those patients who had their attacks soon after injury. In the social and economic rehabilitation of the head-injured patient the severity of injury played an important role, but perhaps even more important was the intelligence of the head-injured men.

Seven patients with post-traumatic epilepsy were divided into those who have had no attacks for 2 years or more and those continuing to have attacks. Although the numbers are small, there is no evidence that the brain waves are more often abnormal in the group with seizures than in the seizure-free group. These findings suggest that the encephalogram has a limited value in the prognosis of post-traumatic epilepsy. The reported data suggest that the end-results of head injury in terms of social, economic, and neurological rehabilitation seem to be dependent not only on the severity of wounding but also on the quality of brain that was damaged.

Parkinsonism Due to Midbrain Compression. L. Oliver. Lancet 2:817-819 (Nov. 14) 1959 [London].

The association of parkinsonian symptoms with brain tumors has been mentioned rarely, but in Oliver's experience parkinsonism is not uncommonly associated with intracranial space-occupying lesions, although its physical manifestations are usually overshadowed. He presents the histories of 3 patients in whom parkinsonian tremor and rigidity were associated with intracranial tumors.

In the first patient, edema of the left cerebral hemisphere was diagnosed because of the onset, 7 days after removal of a left-sided meningioma, of drowsiness, motor dysphasia, papilledema, and return of paresis of the right arm. Midbrain compression was indicated by the positive Hoffman and Babinski signs on the left (ipsilateral) side. The right-sided parkinsonian signs were associated, therefore, with edema of the left cerebral hemisphere and the consequent midbrain compression, and they disappeared as the edema subsided. In the second patient, cerebellar edema developed 2 days after operation, and compression of the brainstem was rapid and severe because the dura mater had been sutured. The tremor and cogwheel and lead-pipe rigidity were probably caused by compression of the midbrain at the level of the tentorial opening, arising from upward herniation of an acutely swollen left cerebellar hemisphere. The third patient had no parkinsonian tremor or rigidity, either before the onset of symptoms due to the tumor or when the manifestations of the tumor were confined to the contralateral side. Ipsilateral tremor and rigidity developed when the level of consciousness declined, the ipsilateral tendon reflexes became brisker than those on the right, and the left plantar reflex became equivocal. One cannot argue that the tremor and rigidity were due to an effect on the globus pallidus, because they were ipsilateral.

Midbrain compression is the factor common to all 3 cases, and is the most likely explanation of the development of parkinsonian manifestations in association with some intracranial tumors. This would conform with current views on the site of the pathological process in both idiopathic and postencephalitic parkinsonism, and it is supported by the effects of lesions produced experimentally in the midbrain of monkeys.

Cardiopulmonary Insufficiency in Myotonic and Progressive Muscular Dystrophy. K. H. Kilburn, J. T. Eagan, H. O. Sieker and A. Heyman. New England J. Med. 261:1089-1096 (Nov. 26) 1959 [Boston].

The authors report on 8 men and 1 woman, between the ages of 22 and 58 years, with myotonic dystrophy, and on 6 men and 2 women, between the ages of 22 and 64 years, with slowly progressive nonmyotonic muscular dystrophy, who were admitted to the neurology service at Duke Hospital and the Veterans Administration Hospital in Durham, N. C. Cardiopulmonary function was assessed in these 17 patients. Twelve patients had dyspnea or other respiratory symptoms. The total lung capacity was reduced in all patients, largely by loss of inspiratory reserve volume. The vital capacity and maximum breathing capacity were impaired to a greater degree in the nonmyotonic patients. The patients with myotonia, on the other hand, showed a reduction in minute ventilation, carbon dioxide retention, and a decrease in ventilatory response to carbon dioxide inhalation. Pulmonary hypertension and a reduced arterial-blood oxygen saturation were also observed in some of the myotonic patients. Oxygen inhalation resulted in further reduction in respiratory minute volume and an increase in carbon dioxide tension in 3 of the 8 patients with myotonia, changes that were not observed in those with nonmyotonic dystrophy. These observations indicate that the syndrome of alveolar hypoventilation may appear in patients with myotonic dystrophy, as it does in those with a variety of other clinical disorders, and is probably the result of weakness of the chest bellows, increased work of breathing due to myotonia, and a disturbance in central respiratory mechanisms.

Carotid Artery Occlusive Syndrome. L. J. Hurwitz, S. N. Groch, I. S. Wright and F. H. McDowell. A. M. A. Arch. Neurol. 1:491-501 (Nov.) 1959 [Chicago].

The development of therapeutic measures for the carotid artery occlusive syndrome makes the early diagnosis of this condition more important. The authors review observations on 57 patients with occlusive carotid disease. The records of 24 of them were obtained from the stroke study files of the Cornell medical and neurological services of Bellevue Hospital, and the records of the other 33 patients were obtained from the New York Hospital. In each of the 24 patients, the diagnosis was confirmed by carotid arteriography. The diagnosis in the 33 patients was established by carotid arteriography in 20 patients, by surgical exploration in 5, and by autopsy in 8. A history of a previous stroke was obtained in 15 patients. Transient ischemic attacks had occurred prior to demonstration of the occlusion in 22 patients. Episodic ipsilateral visual disturbance, alone or with associated contralateral hemiplegia, was described by 10 patients. Somnolence during the prodromal period occurred in 7 patients. The comparative measurements of retinal artery pressure and palpation of the carotid artery in the pharynx were the most reliable bedside diagnostic procedures. Diagnosis without arteriography is considered possible in a majority of instances.

Forty patients received no specific treatment. Eleven patients received anticoagulant drugs for longer than 4 months, and 6 patients had cervical ganglionectomy performed. No inferences can be drawn about the effect of anticoagulants and cervical ganglionectomy from so small a group of patients. The striking variability of the clinical picture and prognosis in individual patients with carotid artery occlusive disease is illustrated in 2 diagrams, one of which graphically records the natural history of patients not treated, and the other the history of patients who were treated.

It is in the stroke with acute catastrophic onset that a large percentage of the deaths or severe residual disabilities occur. In such instances the effects of anticoagulant therapy or surgery on the affected carotid artery are not at present encouraging. More emphasis should be placed on the preceding "minor" cerebral vascular episodes, which are, with the increasing enthusiasm for treatment, more likely to become the event leading to diagnosis. In 5 patients the transient ischemic attacks ceased spontaneously. The course of the disease can be deduced from 19 of the 57 patients, in whom more than 5 years have elapsed since the appearance of the first signs of cerebrovascular disease. Three died within a year; one died within 3 years, and three, 5 years after the first symptom. Three of these 7 deaths were not primarily due to carotid artery disease. The other 12 patients are alive from 5 to 18 years after their first symptoms. The majority of these patients had not received any specific treatment. The great variability of the symptoms of intermittent insufficiency and in the life span of these patients emphasizes the need for well-controlled studies of proposed therapeutic measures.

PEDIATRICS

Staphylococcal Infection in Infancy. C. Isbister. M. J. Australia 2:629-633 (Oct. 31) 1959 [Sydney].

In September, 1958, the New South Wales Department of Public Health, in Sydney, added staphylococcic infections to its list of notifiable infectious diseases. Included were staphylococcic mastitis, staphylococcic pneumonia, and staphylococcic infections occurring in infants under 4 weeks old. Notification of breast abscesses, staphylococcic pneumonia, and infant deaths from staphylococcic infections seemed a matter of urgency, since the main reservoirs of virulent epidemic strains of staphylococci in the community were the maternity hospitals. Owing to the baby's apparent inability to localize infection, quite trivial lesions must be treated with respect. The common infections of the first 2 weeks of life are conjunctivitis, pustular rashes, paronychia, nasopharyngitis with purulent discharge, redness of or discharge from the umbilicus, otitis media; infected skin abrasions, and indurated areas in skin. The more serious infections, tending to occur a little later, are abscesses, cellulitis, osteomyelitis; osteitis and septic arthritis, pneumonia, and pyelonephritis. The author feels that all clinical lesions from which coagulase-positive staphylococci can be cultured must be considered notifiable.

This paper is concerned chiefly with staphylococcic pneumonia in infants and children. Of 22 children with staphylococcic pneumonia whose records were analyzed, the histories of 5 are presented to illustrate the different clinical pictures. The first was an 8-month-old baby with acute fulminating staphylococcic pneumonia, possibly associated with influenza. The postmortem examination revealed extensive hemorrhagic consolidation of both lungs, and hemolytic Staphylococcus aureus, phage type 80, was grown from the lung in pure culture. The second patient was a 2-week-old baby, born in a maternity hospital in which several mothers with breast abscesses were treated at the time. This infant had multiple abscesses in both lungs.

Microscopic examination of sections revealed acute suppurative pneumonia with clumps of cocci in the lungs. Culture of lung tissue yielded a Staph. aureus, phage type 80. The third patient, a 5-week-old infant, had had abscesses since the age of 2 weeks. This infant recovered slowly, and roentgenologic examination revealed a localized pneumonic lesion in one lung. In the fourth baby localized lesions were followed by cyst formation. At the age of 5 months she suddenly became ill, with a very high temperature, grunting respiration, cough, and loose green stools. A roentgenologic examination of the chest revealed a large tension cyst or pneumothorax, and suggested the presence of some pneumonic process in the collapsed lung. The child steadily improved. Hemolytic Staph. aureus, phage type 80, was cultured from empyema fluid. The fifth case was one of pneumonia with empyema formation. A boy, 2½ years old, had a history of a cold with purulent nasal discharge for 2 weeks; this had commenced after his mother returned from the maternity hospital with a newborn baby with a pustular rash. The child's empyema was drained, and he slowly recovered. Hemolytic Staph. aureus was recovered from the empyema fluid and from the mother's breast abscess.

Nine of the 22 children were less than 2 months old, and of these 5 had been circumcised, either while clinical infection was present, or while they were still nasal and umbilical carriers. In all, 17 of the 22 cases could be traced to hospital infection. In 8 of the 9 patients aged under 2 months, local skin lesions or conjunctivitis had been present; the 9th had been circumcised when there were infections among the babies in that hospital. In order to throw further light on the reliability of diagnosis for notification of staphylococcic infections, the author reviewed the records of 69 children, less than 3 years old, admitted with pneumonia to a Sydney hospital in the course of the last 2 years. Among the 30 children who were less than one year old, the staphylococcic origin of the pneumonia was proved in 9; of 12 babies under 3 months, 3 were proved to have the staphylococcic form, and 9 probably had it.

Reduction of Staphylococcal Infection in the Newly Born. A. M. Hill, H. M. Butler and J. C. Laver. M. J. Australia 2:633-634 (Oct. 31) 1959 [Sydney].

In common with maternity hospitals elsewhere, the Royal Women's Hospital, Melbourne, has experienced the growing problem of staphylococcic infections in newborn infants. The following measures were taken to meet this problem: 1. A staphylococcic phage-typing laboratory was set up. 2. A survey of all sections of the hospital staff was made to ascertain the staphylococcic nasal carrier rate. 3. Recruits to the medical and nursing staffs were investigated before commencing duty in the hospital, and, if found to be nasal carriers, they were treated. 4. Nursing disciplines were tightened. Phage typing showed that there was no predominant epidemic strain among the staphylococci recovered from the infected babies or from the staff nasal carriers. But as there was some general correspondence among the various phage patterns of the staphylococci isolated from these 2 groups, nurses who were carriers of Staphylococcus pyogenes were treated by the local application of an antibiotic cream twice a day for one week.

When in spite of these measures the staphylococcic infection rate among babies continued to rise, the infection control committee started to investigate the use of hexachlorophene emulsion for the prevention of neonatal staphylococcic infection. Treatment was at first restricted to babies born in one of the hospital's 2 labor wards and was given only once, before transfer to the postnatal wards. This procedure reduced the number of infected babies in that unit by more than 25%. After this favorable response hexachlorophene emulsion was applied every 48 hours, but it was still given only to babies born in the one labor ward. During the next 4 weeks 230 of 249 babies in this ward were treated, and staphylococcic infection developed in only 4 (1.7%), whereas 5 of the 19 babies (26%) not treated became infected with staphylococci. Furthermore, in the second labor ward in which hexachlorophene emulsion was not used, 78 of 387 babies (20%) became infected with staphylococci. The use of hexachlorophene emulsion also reduced the number of babies who became nasal carriers of pathogenic staphylococci while in hospital.

In the labor ward the nurse swabs the entire surface of the baby with 2 ml. of hexachlorophene emulsion on a cotton swab, paying particular attention to the scalp, the skin creases of the neck, axillas, groins, and natal clefts. This swabbing is repeated with cotton wool moistened with warm tap-water. The lather obtained is wiped off with cotton wool, and the baby is dried. An additional 1 ml. of hexachlorophene emulsion is then wiped over the whole skin surface. In the ward for newborn babies this treatment is repeated at 2-day intervals. The stump of the cord should be covered with a sterile dressing at first. After this dressing is removed, the cord is painted daily with iodine. Apart from a demonstration bath immediately before discharge, no baby is bathed in the hospital. Cleansing, when required, is carried out by sponging with tap-water. Whereas in the 6 months before the use of the hexachlorophene emulsion the incidence of staphylococcic infections was 15%, in the first six months of its full employment it was only 1.3%.

Partial Thoracic Stomach in Childhood. J. B. Burke. Brit. M. J. 2:787-792 (Oct. 24) 1959 [London].

The author reports on 97 boys and 40 girls with partial thoracic stomach who attended the thoracic unit of the Hospital for Sick Children, London, between 1945 and 1955. One hundred thirty-two of the 137 children had a small intrathoracic loculus of stomach, and in the remaining 5 (all girls) the hernia comprised most of the stomach. The main symptoms in the 132 children were vomiting (dating from birth in 77%), hematemesis (in 89%), dysphagia (in 38%), and unsatisfactory gain in weight. Boys predominated in a ratio of 2.7 to 1 and were more severely affected than girls. The prognosis was very good in 74 (91%) of 81 children, aged less than one year. Dysphagia and narrowing of the esophagus were of serious prognostic significance. Of the 132 children with a small intrathoracic loculus, 33 had persistent organic fibrous contracture of the esophagus, 27 had variable narrowing of the esophagus probably due to spasm, and 27 did not have any esophageal narrowing (uncomplicated cases). Mental retardation was present in 10 children, 2 of whom had phenylketonuria and 4 had sucrosuria.

Sixty-eight children were treated medically, and 64 were treated surgically. At the time of follow-up, 9 months to 10 years after the institution of treatment, 41 (60%) of the 68 children treated medically were symptom-free (group 1), 21 (30%) had mild symptoms (group 2), 3 (5%) had fairly severe symptoms but a tendency to improvement (group 3), and only 3 (5%) had persistent severe symptoms (group 4). Thus, 90% were placed in groups 1 and 2 at the time of follow-up, which shows that medical treatment is satisfactory in most cases of partial thoracic stomach. Of the 64 children treated surgically, 24 (38%) were classified at the time of follow-up in group 1, 23 (35%) in group 2, 7 (11%) in group 3, and 10 (16%) in group 4. It is noteworthy that in only 12 of the 64 children treated surgically was there an immediate response to operation with cessation of symptoms. In the others, improvement had sometimes begun before surgical intervention was performed, but more often it was not evident until months or even years afterwards. This makes it difficult to assess the value of surgery. Persistent esophagitis, with or without stricture formation, is to be considered an indication for repair of the hernia. Children without esophageal narrowing and older children with strictures should be given a trial of medical management. The 5 children with a large right-sided intrathoracic loculus, in whom the cardia was found to be above the diaphragm and the hernia comprised most of the stomach, were operated on. Their response to surgical intervention was immediate, with complete relief of symptoms.

Clinical and Epidemiologic Considerations and Research in an Epidemic of Gastroenteritis with Staphylococcic Etiology Among Newborn Infants and Sucklings of a Maternity Ward. N. Nigro and U. Vignolo Lutati. Minerva pediat. 11:975-979 (Sept. 29) 1959 (In Italian) [Turin, Italy].

The authors report a clinical and epidemiologic study made among 35 newborn or suckling babies with hypertoxic gastroenteritis caused by staphylococcic infection, observed during a month in the maternity ward of a hospital in Turin, Italy. Twenty-seven babies who were treated in the hospital were transferred to the pediatric ward. The infection occurred in all instances between the 2nd and 6th days of life. Most of the babies were being breast-fed. All but 3 babies presented loss of body weight that ranged from 270 to 1,110 Gm. (about ½ to 2½ lb.) and was already manifest 2 to 6 days after the appearance of the clinical symptoms. Severe impairment of the general condition (pallor, facies hippocratica, nonelastic cutis with some edema, marked diminution of the panniculus adiposus, and depressed fontanel) and marked toxicity (with involvement of the central nervous system in some cases) were present in all the patients. The gastrointestinal symptoms followed the general symptoms within 2 or 3 days in most instances. Most of the babies presented diarrhea, 22 of the 35 were subject to vomiting, and more than half had fever. A relapse, with symptoms not as severe as in the first episode, was noted in 8 infants. Two infants, 7 and 10 days old, respectively, after clinical recovery from gastritis, suffered from obstructive jaundice. Ten of the 27 infants who were treated at the hospital died; nothing is known of the final outcome of the infection in 8 infants.

Bacteriological examination revealed the presence of a pure culture of massive, gram-positive cocci, which on agar formed round opaque colonies with smooth white margins, 2 to 3 mm. in diameter. The isolated germ grew well in broth at a temperature of 37 C, showing turbidity and sedimentation. On agar the germ developed on the surface, and in gelatin, with liquefaction of the medium at 20 C, it caused acidification and coagulation of milk. The germ likewise caused hemolysis in bacteriological mediums that contained blood (agar and broth); it caused coagulation of rabbit serum at 37 C and acidification (which produced no gas) of glucose, lactose, levulose, saccharose, maltose, mannitol, and glycerin.

The infants derived benefit from treatment with chloramphenicol and tetracycline; those that had relapses benefited from the administration of novobiocin and Signemycin. Total resistance of the cocci to Terramycin, Aureomycin, and the sulfonamides and partial resistance to penicillin and streptomycin were observed. The infection, which the authors believe may have been caused by germs carried into the maternity ward by healthy persons, was highly contagious. Prophylaxis with antibiotics of all those who come in contact with newborn babies who might be infected is advised. Breast feeding may be continued after disinfection of the mother with antibiotics.

High Frequency of Increased Blood Sugar Level in Children with Severe Toxic-Infectious Disease. R. Bulgarelli and R. Bruni. Minerva pediat. 11:895-904 (Sept. 15) 1959 (In Italian) [Turin, Italy].

Increased blood sugar level was observed in 9 of 26 children with a severe acute or subacute toxic-infectious disease. Six patients died of the disease. A meningo-encephalitic disease was present in 7 of the 9 patients with increased blood sugar level. Insulin was given to 3 patients, but without avail; an uncle of one patient and the grandmother of another had died of diabetes. The blood sugar was restored to normal level in the 3 surviving patients; there were no symptoms of diabetes on follow-up inspection after discharge. Correlation between the severity of the disease and the increased blood sugar level seems probable; thus, of 4 patients who had blood sugar levels higher than 200 mg. per 100 cc., only 1 survived. Increased blood sugar level was observed in patients in the final phase of tuberculous meningitis. Hypoglycemia was observed in only one infant, 6 months of age. The authors concluded that there are several factors which cause increased blood sugar level in patients with a severe and acute toxic-infectious disease, but the predominant factor seems to be neurogenic.

Report of a Rare Case of Whipple's Disease in Childhood. R. Bruni and L. Massimo. Minerva pediat. 11:935-943 (Sept. 22) 1959 (In Italian) [Turin, Italy].

A 10-year-old girl was hospitalized with a history of frequent vomiting and of loss of strength, appetite, and weight 2 months before admission. Subsequently her feces changed in consistency, color, and smell; vomiting became more frequent; and oliguria developed. The patient lost 6 kg. (13 lb.) in weight, and her condition remained unchanged during a 2-month hospital stay. Swollen lymph nodes at the root of the mesentery were the only pathological change observed at an exploratory laparotomy. These nodes were removed for microscopic examination. The postoperative course was normal. A combined treatment with pancreatic enzymes, vitamins, and cortisone had been instituted during hospitalization and was continued after discharge. Roentgenologic studies revealed slight dyskinesia of the small intestine, left kidney rotated on its axis with the pelvis in the anterior position, and presence of an ovoid mass between the spleen and the upper pole of the left kidney. Microscopic examination of resected lymph nodes revealed lymphatic and reticulohistiocytic hyperplasia and giant cells with a positive reaction on periodic acid staining. These findings suggested intestinal lipodystrophy (Whipple's disease) in the initial phase. The authors found in the literature only 2 such cases of Whipple's disease.

OPHTHALMOLOGY

Inheritance of Retinoblastoma in Ohio. M. T. Macklin. A. M. A. Arch. Ophth. 62:842-851 (Nov.) 1959 [Chicago].

This study on the family histories of all those children who had been born in Ohio between 1940 and 1956 and who had developed retinoblastoma by the end of 1958 revealed collateral lines affected in 10.5% of those whose cases have been regarded as sporadic. The mode of inheritance agrees with the interpretation that the gene is dominant, but in these families the average penetrance was much lower than that found by other workers. The mutation rate was 1.76×10^{-5} when all sporadic cases were included and 0.63×10^{-5} when only bilateral cases were included. The frequency of the disease, which is based on the ratio of affected persons (including the hereditary as well as the sporadic cases) born within a given time to the number of births occurring in that same period, was about 1 in 23,287 persons who survived to the age of one year.

The risk of producing offspring with retinoblastoma concerns 3 different groups. The first group includes those who know that others among their sibs or close relatives were affected. They should not have children, since their chance of passing on the gene is one-half, and the risk that any one of their offspring will be affected will be one-half times the degree of penetrance which the gene will show in the offspring. The second group includes those who have produced one child with the disease, although they themselves are normal, and there is no known case in the family apart from their affected child. This problem was faced by 145 sibships in this series. In 55 sibships no children were born after the first affected child. In the remaining 90 families in which subsequent pregnancies did occur, 6.67% had one or more affected children. The number of affected children born after the first affected child ranged from 1 to 5. The third group of persons are those who might inquire concerning their risk of bearing affected children, because they themselves represent isolated instances of the disease and have grown to maturity. It might be a phenocopy in them, in which case their children should be normal; it might be a somatic mutation, because most of those who survive have unilateral disease. Of

2 persons representing the third group in this series, each has had one child, and neither child has been affected although still under 3 years of age.

Diabetic Retinopathy and the Pituitary. E. J. Ranke. A. M. A. Arch. Ophth. 62:859-863 (Nov.) 1959 [Chicago].

The author studied the occurrence of diabetic retinopathy in 66 patients (38 women and 28 men) with pituitary tumor. The majority of the patients were between 21 and 40 years of age at the time of recognition of symptoms establishing the clinical onset of the tumor. Thirty of the 66 patients had coexisting diabetes. In 27 of the 30 patients the diabetes was associated with eosinophil tumor, in 2 with basophil tumor, and in 1 with chromophobe tumor. Twenty-one of the 30 diabetics required treatment with insulin; the remaining 9 patients were newly discovered diabetics, as determined by abnormal glucose tolerance tests, and had not required insulin at that time. The time of appearance of diabetes during the course of pituitary tumor proved to be variable. The majority of the patients developed diabetes within the first 6 years after onset of the pituitary tumor. The longer the duration of the pituitary tumor, the greater was the percentage of patients developing diabetes.

Two patients of the entire group of 66 patients had diabetic retinopathy. The 30 patients with pituitary tumor and diabetes were compared with a similar group of 30 diabetic patients without pituitary tumor, but matched identically for age, sex, and duration of diabetes. Results showed that 8 of those patients who had diabetes but no pituitary tumor developed diabetic retinopathy, whereas only 2 of those patients with diabetes and pituitary tumor developed diabetic retinopathy. Pituitary tumors do not seem to contribute to the development of diabetic retinopathy. Whatever the pituitary hormonal influence might be in promoting the development of diabetes, these same diabetogenic factors do not seemingly contribute to the production of diabetic retinopathy. This rarity of diabetic retinopathy in patients with pituitary tumor who develop diabetes mellitus should be considered before pituitary ablation is considered for the removal of diabetogenic factors in a patient with diabetic retinopathy.

Elementary-Body Virus Isolated from Clinical Trachoma in California. L. Hanna, P. Thygeson and E. Jawetz. Science 130:1339-1340 (Nov. 13) 1959 [Washington, D. C.].

The authors present observations on a 36-year-old man, a long-time resident of California, who in January, 1959, complained that his left eye was red, and who had a moderate yellow discharge and a nontender left preauricular lymph node. His physician prescribed 1% chloramphenicol eyedrops, which he instilled for the next 26 days, with some symptomatic improvement. On Feb. 12, a similar conjunctivitis developed in the right eye, with marked photophobia. Neomycin-polymyxin eyedrops were administered for 4 days. On Feb. 16 the inflammation in the left eye suddenly increased markedly, and gross keratitis appeared. Clinical examination on Feb. 17 revealed bilateral papillary hypertrophy, with buried follicles of the upper tarsi, microscopic pannus, corneal infiltrates, and palpable preauricular lymph nodes. Scrapings from the upper tarsal conjunctivas showed many inclusions typical of trachoma. Bacterial cultures were negative, but a virus was isolated from conjunctival scrapings by injection of the material into the yolk sac of embryonated eggs. Morphologic and serologic studies identified the virus as belonging to the psittacosis-lymphogranuloma group. The elementary bodies conformed in size and staining properties with those grown by others from trachoma patients. Four monkeys (Macaca cynomolgus) were inoculated in one eye with a 20% yolk-sac suspension of 6th-passage virus. Follicular conjunctivitis developed in all monkeys 2 to 6 days later, and the conjunctival scrapings contained many typical inclusion bodies. The patient was treated with topical application of tetracycline and oral administration of methylsulfapyridazine (500 mg. daily) for the next 8 weeks, with gradual disappearance of all clinical and microscopic signs of trachoma. This appears to be the first isolation of an elementary-body virus of the psittacosis-lymphogranuloma group ("trachoma virus") from a typical case of trachoma arising in the United States.

THERAPEUTICS

A Comparison of the Diuretic Action of the Chlorothiazide Analogues. D. S. Young, T. M. Forrester and T. N. Morgan. Lancet 2:765-768 (Nov. 7) 1959 [London].

The authors compared the diuretic action of chlorothiazide, hydrochlorothiazide, and hydroflumethiazide in 10 healthy male medical students without evidence of renal disease. These men were allowed a fixed and known fluid intake. The urine of each man was collected over a period of 24 hours on 4 separate occasions. In the first control period no drug was given, and in the subsequent 3 periods the effects of 2,000 mg. of chlorothiazide, 150 mg. of hydrochlorothiazide, and 150 mg. of hydroflumethiazide were compared. At least 7 days elapsed for each man between successive experiments to allow the restoration of normal body-fluid composition. The results showed that all 3 drugs caused diuresis with similar changes in the composition of the urine, except that hydrochlorothiazide and hydroflumethiazide were effective in smaller dose and caused less potassium and bicarbonate loss than chlorothiazide. The actions of hydrochlorothiazide and hydroflumethiazide were more prolonged than that of chlorothiazide, particularly concerning the excretion of sodium and chloride. The prolonged action and the smaller effective dose of hydrochlorothiazide and hydroflumethiazide can be explained by the finding that chlorothiazide is less completely absorbed by the intestine and more rapidly eliminated in the urine than are hydrochlorothiazide and hydroflumethiazide.

Antimicrobial Therapy of Non-Tuberculous Pulmonary Infection. C. E. van Rooyen and R. C. Dickson. Canad. M. A. J. 81:706-710 (Nov. 1) 1959 [Toronto].

The authors state the guiding principles of antibiotic therapy in nontuberculous pulmonary infections: (1) to know the natural history of the disease under treatment; (2) to know how this is modified by antibiotics or chemotherapy; and (3) to take the necessary steps to find out why, in certain cases, the probable course of the disease cannot be arrested. A careful watch should be maintained on pulmonary changes, since no antibiotic administered by any route can penetrate a thickened pleura or a lung abscess.

The merits of antibiotics currently used to treat infections due to penicillin-resistant organisms are listed, as established at the Sixth Symposium on Antibiotics held in Washington, D. C. Kanamycin is active against staphylococci, Escherichia coli, and other organisms, but not against streptococci, pneumococci, and Pseudomonas organisms; its toxicity is manifest on the 8th nerve and on the kidneys. Erythromycin propionate acts best against rapidly multiplying organisms, although resistance can develop in vitro during the treatment. Vancomycin is the most potent antibiotic against resistant staphylococci; its intravenous administration to children is sometimes accompanied by painful phlebitis. Ristocetin has a much more powerful effect than erythromycin and penicillin. Novobiocin has a great value in severe staphylococcic infection.

The authors call attention to the problems resulting from antibiotic therapy. They report the successful treatment of 70 patients with bronchitis to whom tetracycline was administered in the dose of 250 mg. every 6 hours during 5 days, in a total dose of 5 Gm. Examination of the stools during the treatment showed temporary suppression of normal intestinal flora and slight increase in Candida albicans without evidence of moniliasis; staphylococci appeared in the stools without the onset of diarrhea. The sulfonamides, relegated to a second plane by the new antibiotics, represent a useful second line of defense against infections. The use of antibiotics as a preventive therapy is not recommended. So far as lung infections are concerned, prophylactic antibiotics may do more harm than good in 3 situations: (1) certain postoperative states; (2) bulbospinal poliomyelitis with respiratory complications; and (3) cerebrovascular accidents. The association of cortisone with antibiotics may suppress the inflammatory defense mechanism and so aggravate the severity of pulmonary infection. In pneumonia this association is beneficial, provided that an effective antibiotic is administered.

A Comparison of Prednisolone with Aspirin or Other Analygesics in the Treatment of Rheumatoid Arthritis: Report by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, ACTH, and Other Therapeutic Measures in Chronic Rheumatic Diseases. Ann. Rheumat. Dis. 18:173-188 (Sept.) 1959 [London].

A study is reported on the effect of prednisolone, compared with the effect of aspirin or other analgesics, in the treatment of 84 patients with rheumatoid arthritis. A few patients defaulted, died, or were withdrawn from the trial, and the results of 2 years of treatment are based on the analysis of 77 patients, 41 of whom were originally allocated to prednisolone therapy and 36 to analgesics. The patients treated with prednisolone showed an early significant improvement in both clinical and laboratory indexes of inflammatory polyarthritis, and this improvement, though less, was still present to a significant extent at the end of 2 years. In the patients treated with analgesics, the frequency of radiologic signs of erosive joint disease in the hands and feet increased significantly over the 2 years, whereas there was no significant change in the group treated with prednisolone. In many patients treated with prednisolone, the agglutinating titer in the sheep-cell test rose during the 2 years of treatment, whereas such a rise occurred in only a few patients treated with analgesics. Two patients treated with analgesics died of heart failure. Five patients treated with prednisolone developed major complications—2 developed psychosis and 3, peptic ulceration. These major complications occurred in patients receiving a daily dose of 20 mg. (or more) of prednisolone. Patients receiving prednisolone also gained weight, and showed some rise in blood pressure and a tendency to mooning of the face. During the trial the mean daily dose of prednisolone was gradually reduced from 17.4 to 10 mg., and more than half of the patients on prednisolone therapy were also receiving aspirin or other analgesics.

The joint committee believes that the administration of prednisolone, instead of, or in addition to, analgesics, to certain patients with rheumatoid arthritis for a period of 2 years will, on an average, improve their functional capacity and general well-being and reduce the incidence of erosive joint damage. More patients, however, are likely to show a rise in sheep-cell agglutination titer, and the significance of this therapy for the future of the patients is not yet known. Undesirable side-effects are likely to occur if the daily dose of prednisolone approaches 20 mg. per day. For the committee, the highest acceptable dose for long-term therapy is 10 mg. of prednisolone per day.

Further Experience with Oral Therapy in Diabetes. K. L. Granville-Grossman, S. Crawfurd, M. F. Crowley and A. Bloom. Brit. M. J. 2:841-847 (Oct. 31) 1959 [London].

The authors report on 113 patients with diabetes mellitus, 30 of whom, between the ages of 34 and 89 years, were treated with metahexamide, a sulfonylurea compound; 75, between the ages of 38 and 86 years, were treated with chlorpropamide; and 8, between the ages of 47 and 75 years, were treated with dimethylbiguanide. In 20 of the 30 patients, the diabetes was well controlled by an initial dose of 300 mg. of metahexamide daily, later reduced to 50 to 200 mg. of the drug daily. On this dose the blood sugar levels remained within the normal range, and the urine became virtually free of sugar. The remaining 10 patients were therapeutic failures. No rash, gastrointestinal upset, or evidence of blood dyscrasia was observed after treatment with metahexamide, and no patient complained of symptoms referable to hypoglycemia. Jaundice, however, was observed in one patient after treatment with this drug. Chlorpropamide was successful in controlling the diabetes in 50 of the 75 patients treated with this drug. The blood sugar level remained within normal limits, and the urine became free from sugar for most of the day while these patients were receiving the drug, which was given in one dose of 500 mg. in the morning daily; the dose was reduced to 200 mg. daily if a satisfactory hypoglycemic response was obtained. Twenty patients were therapeutic failures, and in 5 patients administration of chlorpropamide was discontinued because of intercurrent illness or side-effects consisting of a generalized rash suggestive of sensitivity dermatitis. Seven of the 8 patients treated with dimethylbiguanide had a satisfactory hypoglycemic response to a daily dose of 1 to 3 Gm. of the drug. Five of the 8 patients complained of nausea, vomiting, or diarrhea, necessitating withdrawal of the drug in 3.

These findings suggest that metahexamide is a well-tolerated hypoglycemic agent, effective in patients with mild diabetes mellitus with onset at maturity. Its action is more sustained than that of tolbutamide, so it can be administered once daily. Chlorpropamide is a more effective oral hypoglycemic agent than tolbutamide, and needs be given only once a day. It is well tolerated, but occasionally gives rise to sensitivity reactions. Dimethylbiguanide is an effective hypoglycemic agent but is not well tolerated by mouth. Half-life studies on metahexamide showed that the drug disappeared from the plasma more rapidly in normal persons than in patients with diabetes mellitus. Many patients with diabetes mellitus, particularly those with a recent onset of the disease, remained controlled by simple dietary restriction alone after a 6-week course of oral therapy, though the length of remission varied. Three patients with diabetes mellitus, who failed to respond to either metahexamide or chlorpropamide or phenethylbiguamide (Phenformin) when given separately, were stabilized on a combination of chlorpropamide or metahexamide with Phenformin.

Chlorpropamide in the Treatment of Diabetes Mellitus. D. Jackson and W. Oakley. Lancet 2:752-754 (Nov. 7) 1959 [London].

The authors report on 126 patients with diabetes mellitus, who were treated with chlorpropamide (Diabinese) at the diabetic clinic of the King's College Hospital in London. Of the 126 patients, 54 had mild diabetes not requiring insulin therapy, 48 had been controlled with less than 40 units of insulin per day, 13 had required more than 40 units of insulin per day, and 11 had acute ketotic onset. Forty-two of the 54 patients, 35 of the 48 patients, 6 of the 13 patients, and 6 of the 11 patients, i. e., a total of 89 patients, obtained satisfactory control of their diabetes on chlorpropamide therapy. The initial dose of chlorpropamide given to these patients varied from 250 to 375 mg. The change from insulin to chlorpropamide was effected in 2 different ways. In 33% of the patients the dose of insulin was reduced by 50%, and 100 to 250 mg. of chlorpropamide was administered together with the reduced dose of insulin, which was further reduced over a period of 7 to 14 days if good results were obtained. In the remaining patients, the insulin administration was stopped completely, and the first dose of chlorpropamide administered on the following day. The carbohydrate allowance in the patients' diet varied from 90 to 200 Gm. per day.

The maximum period of treatment with chlorpropamide in these patients was 7 months, and so far only 5 have had a relapse after a period of good control on chlorpropamide therapy. Two of these 5 patients were young ketotic diabetics who were started on chlorpropamide therapy during the period of increased carbohydrate tolerance which often follows the institution of insulin therapy, and in the other 3 patients there were complications caused by some unrelated medical condition. Of 17 patients who had relapses on tolbutamide treatment, 15 responded well to chlorpropamide. These data show that chlorpropamide has a greater range of activity than tolbutamide and is effective in patients in whom relapses occur on tolbutamide therapy. The incidence of toxic effects of chlorpropamide is low when the maximum dose does not exceed 375 mg. per day. The patient's age and the duration of diabetes mellitus had no bearing on the response to chlorpropamide in these patients.

Both tolbutamide and chlorpropamide were used in the treatment and suppression of steroid-induced diabetes in 5 patients. It is too soon to analyze completely the results obtained in these patients, but preliminary results suggest that steroid-induced diabetes can be suppressed by the administration of either tolbutamide or chlorpropamide in the early stages of the disease.

Nitrogen Mustard and Adrenocorticotropic Hormone in the Management of Patients with Incurable Carcinoma. M. W. Wolcott and W. A. Shaver. South. M. J. 52:1375-1379 (Nov.) 1959 [Birmingham, Ala.].

Eighty patients with far-advanced cancer, with either focal or distant metastases, were given a combined corticotropin (ACTH) and nitrogen mustard therapy. Nitrogen mustard was administered in daily doses of 0.1 mg. per kilogram of body weight for 5 days; corticotropin was given intramuscularly in doses of 60 mg. every 6 hours, beginning 18 hours prior to the first dose of nitrogen mustard and continued for 5 days, and then in decreasing doses over the next 2 days. Supportive treatment with antibiotics, blood transfusions, and intravenously administered fluids was given as indicated. Usually, the combined treatment was resumed after an interval of 4 to 6 weeks, but this interval was increased to 2, 3, and 4 months in some patients who showed a good response to treatment. In this series of 80 patients other treatments were also applied, such as palliative surgery in 31 and roentgenotherapy in 50. Excellent results were obtained in 10% of the patients. One patient with carcinomatosis of the peritoneal cavity and another with lymphosarcoma are both living and well after 3 years. Three patients with carcinoma of the lung are living, 2 of these after a year and a half and 1 after 6 months, without evidence of recurrence at this date. Fifteen patients (18.7%) had good palliation; all have died. Nineteen patients (23.8%) had fair palliation; all have died. Thirty-eight patients (47.5%) had poor palliation; all have died.

The authors believe that the combined treatment with corticotropin and nitrogen mustard has a limited, but definite, place in the palliation of advanced cancer. Its value was more apparent in patients with bronchogenic carcinoma. The best results were obtained in patients in whom nitrogen mustard therapy was immediately given after surgical treatment. A failure to obtain some relief with the first course of treatment with nitrogen mustard and corticotropin contraindicates subsequent courses. The toxicity of nitrogen mustard was reduced by the concomitant use of corticotropin.

PATHOLOGY

Post Mortem Studies on Coronary Atherosclerosis in One Population Group. D. M. Spain and V. A. Bradess. Dis. Chest 36:397-406 (Oct.) 1959 [Chicago].

Postmortem studies were made on the hearts from consecutive Medical Examiner's autopsies in Westchester County, New York. The coronary arteries were sectioned at 2-mm. intervals, examined, and graded by an observer who had no knowledge of the sex, age, race, occupation, and mode of death of the persons in question. After this examination the findings were related to the respective categories of data. The incidence of coronary atherosclerosis in sedentary and physically active "normal" persons was studied in men, between the ages of 30 and 60 years, who had died suddenly in traffic or industrial accidents. The sedentary group was represented by 82 specimens, and the active life group by 84. Three degrees of atherosclerosis were established, and their distribution studied in relation to six 5-year age groups. The incidence of the different degrees of atherosclerosis was similar in both the sedentary and the active life samples of each age group. The distribution of the average grading of coronary atherosclerosis was not significantly different in relation to the 2 variables.

The relative incidence of atherosclerotic and thrombotic coronary occlusion in sudden death was studied in the entire series of autopsies. There were 367 men and 43 women, with the great majority in the 39-to-69-year age bracket. In 50 of the 310 cases of atherosclerotic occlusion and in 17 of the 100 cases of thrombotic occlusion, there had been physical activity prior to the attack, which means an over-all percentage of 30%. Among the 43 women, atherosclerotic occlusion had occurred in 7 under 50 years of age and in 24 over 50 years, whereas the number of thrombotic occlusions was, respectively, 3 and 9. Among the 277 men who had died of atherosclerotic occlusion, 68 had had infarction; 41 had performed some strenuous activity prior to death; 11 had both had infarction and had exerted strenuous activity. Of the 90 men who had died of thrombotic occlusion, 31 had had infarction and 15 had had strenuous activity; in 8 of these 15 the exertion was associated with infarction. Six of those with atherosclerosis and 2 of those with thrombotic occlusion had performed some unusual strenuous activity. The authors conclude that strenuous physical activity prior to sudden death from either atherosclerotic or thrombotic occlusion is less frequent than is generally believed, and does not appear to be an important factor, except in occasional instances. Acute coronary thrombosis is primarily a complication of, and intimately related to, the atherosclerotic process.

Three groups of autopsied persons were studied in relation to the comparative degree of aortic and thrombotic atherosclerosis. In the first group there was a lower grading of aortic than of coronary atherosclerosis; in the second there was an equivalent grading of both types; and in the third there was a higher grading of aortic than of coronary atherosclerosis. The incidence of these gradings was analyzed with reference to 2 age groups—those from 30 to 50 years and those from 50 to 70. Of the 46 women in the 30-to-50-year age group, 21 had a higher degree of aortic than of coronary atherosclerosis, 19 had approximately the same degree of both, and 5 had a higher degree of coronary than of aortic atherosclerosis. Among the 77 men in the same group, these proportions were reversed. In the over-50 age group the relative gradings of coronary atherosclerosis in the women tended to approach those in the men, and the relative relationship of coronary to aortic atherosclerosis was almost equally divided in the 2 groups. The general and the specific differences indicate that estrogens are a factor in the atherogenic process and may be more specifically related to coronary than to aortic atherosclerosis. They may also indicate that a certain local vascular factor is important in determining the differential rate of atherogenesis.

Autopsy data on 50 suicides were compared with the data on 50 accidental deaths. The absolute and relative incidences of coronary atherosclerosis were very similar in both groups. Since suicide is supposedly an indicator of emotional disturbance, these results do not support the belief that emotional stress had an important role in the pathogenesis of atherosclerosis, although there are other aspects, such as the effect of stressful situations on persons with underlying advanced coronary atherosclerosis, which were not included in this study.

Primary Heart Tumors: Two Cases. K. Maurseth. Nord. med. 62:1452-1455 (Oct. 1) 1959 (In Norwegian) [Stockholm].

Primary heart tumors are rare and are seldom diagnosed before death. Primary benign heart tumors are 3 to 4 times as frequent as the malignant. The primary malignant tumors of the heart described have been sarcomas of various types, equally apportioned between ventricle and atrium. About half of the primary benign heart tumors are myxomas, which occur almost exclusively in the atrium and are mostly polypoid. Rhabdomyomas, fibromas, lipomas, and angiomas have also been reported. Most heart tumors are accidental findings. Often even large tumors give few symptoms. The first of the 2 cases of primary heart tumor seen in the Rikshospital in Oslo in 1958 was that of a woman, aged 32 years. Cerebral symptoms dominated the picture. Angiography of the carotid showed an expansive process of walnut size in the right parietal-occipital region, with presumably several smaller similar processes. The excised plum-sized tumor was histologically diagnosed as metastasis from a slightly differentiated malignant tumor. Death soon ensued. The polypoid heart tumor found at autopsy almost filled the left atrium and extended through the mitral ostium into the ventricle. The histological diagnosis was fibrochondroangioma. In the second instance, in a man, aged 50 years, who died of a reticulosarcoma, autopsy disclosed a tumor on the anterior surface of the right ventricle. The diagnosis was cavernous hemangioma. Angiography is the best aid in the diagnosis of polypoid intracardial tumors.

Observations on Thrombosis and Endothelial Repair Following Application of External Pressure to a Vein. H. R. Robertson, J. R. Moore and W. A. Mersereau. Canad. J. Surg. 3:5-16 (Oct.) 1959 [Toronto].

The effects of pressure applied to the external surface of the inferior vena cava were observed in an experimental study on 450 rats. By varying the amount and duration of pressure, it was possible to estimate the fragility and the recuperative power of the endothelium as well as the degree of injury necessary to produce thrombosis. The animals were anesthetized with pentobarbital (intraperitoneally), and the vena cava was exposed by gently displacing the intestine. A sterilized pressure foot, approximately 4 mm. in diameter, was applied to the surface of the vein. If the pressure was to be maintained for more than a few minutes, the abdomen was closed about the pressure foot in order to prevent dehydration. For observation of the immediate effects, the vein was stained and fixed as soon as the pressure foot was removed. For observation of progressive changes, groups of animals were anesthetized and their veins prepared at different intervals after removing the pressure and closing the abdomen. Eighty-six specimens, prepared and examined in groups at different intervals, served as controls.

No change was noted in the venous endothelium under a 10-second-long pressure of a 5-Gm. weight. A weight of 10 Gm. applied for 30 seconds, or 50 Gm. applied for 10 seconds, regularly produced localized lesions. In 11 rats examined 5 or more hours after removal of the weight, the endothelium appeared normal, which suggests that the changes are reversible. Weights of 100 and 200 Gm., applied to the vena cava during 1 hour and 3 hours, respectively, had fundamentally the same effects, namely, destruction of the endothelial layer with frequent formation of platelets and white blood cell thrombi. Repair by means of endothelial cellular ingrowth was observed in 54 rats to whose venae cavae a 100-Gm. pressure was applied for one hour. At 24 hours the first signs of repair were seen in the development of nucleoli in the endothelial cells surrounding the injured zone. By 48 hours mitotic figures had appeared in the surrounding cells, and actual division could be seen. By 144 hours mitosis had ceased, a few nucleoli and endothelized thrombi remained, and the cells were still closely packed and jumbled.

The authors suggest that the cause of thrombosis in humans may in certain cases be traced to the effects of direct pressure upon the vein. This may be the mechanism of thrombophlebitis occurring in persons who sit in a cramped position for a long time, or in those whose calves are compressed, as when they lie on an operating table. It is probable that as a result of unnoticed injuries the process of endothelial damage, thrombosis, and repair is constantly taking place in various parts of the body. The fact that thrombophlebitis is not an extremely common condition strongly suggests that trauma alone is seldom sufficient for propagation of the thrombus, which is the essential feature of thrombophlebitis. Some other factors, still unidentified, must be present in order to permit or to stimulate progression of the thrombus that may have been initiated by trauma.

RADIOLOGY

Roentgenologically Controlled Placement of the Needle in the Trigeminal Root for the Treatment of Tic Douloureux. T. Perl and A. Ecker. Am. J. Roentgenol. 82:830-839 (Nov.) 1959 [Springfield, Ill.].

Tic douloureux is a type of paroxysmal facial pain, and it occurs usually in patients over 40 years of age. There is a trigger zone, usually in the skin or mucous membrane served by the second and third divisions of the trigeminal nerve, the lightest touch of which precipitates the pain. The production of analgesia of the trigger area usually prevents further attacks. The authors describe a method of inserting a needle into the posterior root of the gasserian ganglion in order to inject the area with alcohol and produce numbness. A preliminary roentgenographic study is first made to determine the exact position of the head and the entry point of the needle. After the needle is inserted, further roentgenographic study indicates the relationship of the needle tip to the base of the skull and permits accurate adjustment of its depth. Procaine (2%, 0.03 cc.) is then injected to determine the position of the needle within the posterior root. Therapeutic injections of 0.05 cc. of absolute alcohol are finally made as indicated by careful sensory and motor testing.

The authors have used this method in 61 patients with trigeminal neuralgia, one of them with bilateral trigeminal neuralgia, during the period from October, 1954, through October, 1958. Numbness was produced in all patients, and pain was completely relieved initially. Pain recurred in 10 patients, and another injection was necessary. One of the patients underwent surgical rhizotomy later. Eight patients presented total corneal anesthesia, 2 presented brief periods of superficial corneal abrasion, but in no case was there keratitis or the need for tarsorrhaphy. Corneal sensation returned after one year in one patient. About half of the patients have had postinjection paresthesias; of these, only 3 were severe.

A Safe and Practical Intravenous Method for Abdominal Aortography, Peripheral Arteriography and Cerebral Angiography. I. Steinberg, N. Finby and J. A. Evans. Am. J. Roentgenol. 82:758-772 (Nov.) 1959 [Springfield, Ill.].

A safe and practical intravenous method of abdominal aortography, peripheral arteriography, and cerebral angiography, based on physiological principles learned during angiocardiography, is described. By this method organic iodides are injected rapidly and simultaneously in both arms with special syringes attached to Robb-Steinberg cannulas; the patient is ordered to "stop breathing," and a 2-second exposure for abdominal aortography is made. If peripheral arteriography is desired, another exposure may be made, either with a portable roentgenographic apparatus or with another tube. Standard grid cassette technique for lower extremity roentgenography suffices. The procedure may be repeated after a short interval if the patient has tolerated well the first procedure. If the peripheral circulation at the bifurcation of the iliac arteries is desired, the Bucky grid carriage may be shifted to include the extremities, and another injection made.

The first successful abdominal aortogram, with rapid, bilateral, simultaneous intravenous injection of concentrated contrast material, was made in March, 1959. Twelve additional patients, reported on in this study, have been seen since then, and in each instance the abdominal aorta and its branches were visualized. Since the submission of this study for publication in May, 1959, the method has been successfully employed in additional cases, raising the total number to 52. The abdominal aorta and peripheral arterial circulation were visualized in every case.

The optimal dose of concentrated contrast material has been established by the authors at 1 cc. per kilogram of body weight. Eleven of the 13 patients reported on suffered a mild and transient reaction to the injection. Reactions can be diminished markedly if a calm, reassured, nonapprehensive attitude is used. Aneurysmal and occlusive disease of the abdominal aorta and branches can be readily diagnosed by this method, facilitating the appropriate treatment for each patient. Cerebral angiography via the intravenous route, especially when biplane studies are made, will open a new field of diagnosis, and vascular malformations and displacement of cerebral structures may furnish clues to hitherto unrecognized syndromes of brain disease. Angiographic studies to locate subdural and cerebral hematomas after cerebrovascular accidents may become routine. The method described has distinct advantages over the translumbar, carotid, and vertebral arterial injection routes, which have sometimes been associated with serious complications and occasionally with death. The intravenous method of abdominal aortography and peripheral arteriography may be employed in almost every radiologic department, since conventional roentgenographic equipment is all that is required.

Hyperostosis of the Basilar Part of the Cranium in the Clinical and Roentgenologic Picture of Thalassemia. E. Durando and E. Grassi. Minerva pediat. 11:905-909 (Sept. 15) 1959 (In Italian) [Turin, Italy].

The authors report on 5 patients, aged between 1 and 3 years, with thalassemia or familial erythroblastic anemia (Cooley's anemia). Pallor appeared from the first days of life in 3 patients, from the third month in 1, and from the fourth month in 1. Retarded body growth was noted in 2 children. Roentgenologic examination of the cranium revealed thickening of the frontal bone in one patient, of the frontal and occipital bones in one, and of the vault of the cranium in one. It also showed marked hyperostosis of the vault of the cranium and, in particular, of the frontal and parietal bones in one. The main roentgenologic feature common to all 5 patients was the hyperostosis of the basilar part of the cranium. This lesion is often more pronounced than any other skeletal change. The authors believe that hyperostosis of the basilar part of the cranium is an essential, and not a secondary (as hitherto considered), diagnostic feature of Cooley's anemia.

The Clinical Significance of Arthrography of the Humeroscapular Joint. M. J. Kingma. Arch. chir. neerl. 11:261-265 (no. 3) 1959 (In English) [Arnhem, Netherlands].

The author, in collaboration with the radiologic department of the Wilhelmina Hospital in Amsterdam, investigated the problem of whether arthrography of the humeroscapular joint would improve the diagnosis of lesions of this joint, particularly the rupture of the rotator cuff. He shows that the radiologist can estimate the size and localization of the rupture. In addition, the radiologist will attempt to obtain by planigraphy or stereography exact information on the localization and extent of the defect. Thus, arthrography is capable of demonstrating or excluding complete cuff rupture. The author had occasion to compare arthrographic findings with surgical findings in 17 instances; the arthrographic indications were always confirmed. The objection might be raised that complete cuff rupture can well be diagnosed without an arthrogram. This is true only in cases that show the classical picture with all its symptoms. In other cases a diagnosis based exclusively on clinical findings is unreliable. Arthrography is indicated in cases in which abduction of the arm is still difficult 2 or 3 weeks after a trauma of the shoulder. Arthrography is also indicated in long-standing shoulder complaints.

Calcified Adrenal Cysts. A. J. Palubinskas, W. R. Christensen, J. H. Harrison and M. C. Sosman. Am. J. Roentgenol. 82:853-861 (Nov.) 1959 [Springfield, Ill.].

The cases of 4 patients (2 men and 2 women), 46 to 55 years of age, with benign adrenal cysts are reported. Approximately 80 cases of this disease have been published in the literature, and in only 3 instances was a correct preoperative diagnosis made on the basis of roentgenologic findings; in 2 of them, the most important feature was a thin laminar calcification of the cyst wall. The 4 cases reported by the authors showed this characteristic calcification. Symptoms or the past history of the patients are seldom revealing as far as the diagnosis is concerned. The diagnosis in all 4 cases reported here, and in some of the cases reported in the literature, was made on the basis of a mass, observed on roentgenologic examination, localized in the adrenal region, the periphery of which was outlined by curvilinear calcification. The incidence of calcified adrenal cysts seems to be 50% higher in women than in men; they occur in about equal numbers on the right and left sides. The majority of the cases concern patients in the 30-to-60-year age group, but the finding has been reported in all age groups from 2 months to 70 years. Reported size has varied from that "of a boy's marble" up to 30 cm. in diameter. The cysts may be unilocular or multilocular, and the contents vary from translucent fluid to dark gelatinous material mixed with tissue debris. The wall components are generally dense fibrous connective tissue, which may be hyalinized or may rarely show amyloid degeneration. The thickness of the wall is generally 1 to 5 mm., though some walls measuring 1 and 3 cm. have been reported. A variety of other cellular elements have been reported as components of the wall.

One-third of the cases of calcified adrenal cysts noted in the English literature show calcification microscopically, and in one-sixth this calcification is visible [illegible]. The paucity of reports in [illegible] manifestation of the clinical silence characteristic of these cysts rather than of their true rarity. The authors believe that, if a thin laminar calcification at the periphery of a soft tissue mass in the suprarenal gland is observed on roentgenologic examination, the demonstrated tumor is cystic and benign, and arises in or from the adrenal gland.

BOOK REVIEWS

Pediatric Pathology. By Daniel Stowens, M.D., Pathologist, Children's Hospital Society of Los Angeles. Cloth. $20. Pp. 676, with 374 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2, 1959.

As stated in the preface, there is a need for a book devoted to the anatomy of diseased children. Only occasionally are pathologists given the opportunity of spending most of their time studying diseases of children. Much of the information and photographic material presented here was collected during the years the author spent as registrar of the American Registry of Pediatric Pathology at the Armed Forces Institute of Pathology, Washington, D. C. A certain amount of clinical material is included with most subjects discussed to help correlate the morbid anatomy with the clinicians' experience. The book is predominantly concerned with processes about which there has been recent rapid development of knowledge and other processes that are still in the research-hypothesis stage. The author avoids discussing many subjects with the statement that these problems are already amply covered in existing texts. This leaves most of the work for the more important description of pathology of diseases that have recently become more completely understood. Where older hypotheses and clinical experience are unable to explain known anatomic distortion, the author presents hypotheses that do not conflict seriously with known clinical, laboratory, and research findings. This should be of great help to those who must sometimes explain seemingly unrelated phenomena in the course of children's diseases. Some of the author's hypotheses and descriptions may arouse howls of disagreement, but he is refreshingly aggressive in suggesting that they serve the purpose of calling attention to problems that previously did not seem to exist. The discussion of sudden death associated with respiratory inadequacy in infants is particularly striking.

Some of the rare diseases are discussed in glossary form, but the bibliography for such processes is usually sufficient to indicate sources of further reference. The diseases considered occur all over the world. The text is abundantly illustrated with the usual excellent detailed photographs from the Armed Forces Institute of Pathology. The pictures are mostly photomicrographs and will be of greatest value to the pathologist, although they should be of help to the clinician who conscientiously tries to understand the anatomy associated with abnormal clinical and laboratory findings. This book should help pediatricians and general practitioners to realize that the pathologist can be helpful in the study of some diagnostic problems. The appendix consists of a classification of the diseases of the first 10,000 patients about whom information is entered in the files of the American Registry of Pediatric Pathology. Most of this information was collected from 1954 to 1956.

The style is pleasant. The detailed analyses of particular problems are still found principally in medical journals, but this book should fill a serious need for a general textbook on the extent and character of pediatric pathology and should be in the library of all pediatricians, pathologists, county medical societies, and hospitals.

Jewish Medical Ethics: A Comparative and Historical Study of Jewish Religious Attitude to Medicine and Its Practice. By Rabbi Dr. Immanuel Jakobovits. Cloth. $6. Pp. 381. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1959.

For all the years that man has been on earth, disease has been one of his chief enemies. Every culture has shown a lively interest in the healing arts. Elements of magical, demoniacal, and rule-of-thumb practices are common to all of them. The nature of the culture determines some attitudes. The Greeks, for instance, believed that illness marred the perfection of "whole man" and was thus a misfortune or a catastrophe. The Jews, while they shared the common experience of primitive peoples and borrowed much from their neighbors, gave their outlook on medicine a strongly religious tinge. Their monotheistic belief led them to think that sickness was sent by God as a punishment for sins. Castiglioni has pointed out that this reduced the number of superstitions about malignant demons, animistic concepts, and superstitious and magical practices. The Creator was compassionate, however, and, if approached through his priests with a contrite heart, was the source of healing. These attitudes influenced the development of Jewish medical and hygienic concepts.

From these beliefs sprang a tremendous body of regulations intended to insure the recovery from illness and the maintenance of bodily and spiritual health. It existed as an extensive code throughout the ages and regulated the hygiene of all the Jewish people. It was concerned with the control of epidemics through bathing and many other practices. The regulations, which have to do with ritual slaughter, foods which may not be eaten, circumcision, and purification after menstruation, are followed by the Orthodox Jew to this day. The author is concerned with the ethics of Jewish medical

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These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

practice as determined by Jewish sacred literature and tradition. He makes it clear that all medicine, while largely based on science, is and must remain an art with strong moral overtones. This the Jews brought about by way of their religious beliefs. No one should try to make medicine wholly scientific. The attempt would fail, anyway, but would nevertheless remove the properly strong overtones of compassion and high regard for the dignity of man's estate. These attempts can and do lead to the excesses of the so-called human experimental procedures, as seen, for example, in the Hitlerian regime. This interesting and scholarly treatise may be read with benefit and pleasure by all who are interested in the moral and ethical aspects of medicine.

Diabetes mellitus. III. Kongress der International Diabetes Federation Düsseldorf, 21.-25. Juli 1958: Proceedings, Verhandlungen, Comptes Rendus. Herausgegeben von Prof. Dr. K. Oberdisse, Direktor der II. Medizinischen Klinik und Poliklinik der Medizinischen Akademie Düsseldorf, und Priv.-Doz. Dr. K. Jahnke, Oberarzt der II. Medizinischen Klinik und Poliklinik der Medizinischen Akademie Düsseldorf. Cloth. 175 marks; $41.65. Pp. 799, with 225 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

Participants in the Congress here reported represented 42 nations, and the contributions are printed in English, German, or French. The main subjects considered were (1) new theoretical knowledge of carbohydrate metabolism, (2) the diabetic angiopathy, (3) the oral treatment of diabetes mellitus, and (4) the problems presented by the diabetic child. Additional subjects presented at the round table included diabetes and pregnancy and methods of determining amounts of insulin, insulin antibodies, and insulin inhibitors in the blood. The discovery of diabetes in patients (the so-called detection drive), the care and aftercare of aged patients, and the demography of the diabetic were discussed in special sessions. The Banting Memorial Lecture entitled "Zur bedingten Gesundheit des Diabetikers" was delivered by Professor Gerhardt Katsch of Greifswald and emphasized the necessity of continuous medical control of diabetes.

More than 200 communications from 350 authors provided a comprehensive summary of the results of recent experimental and clinical investigations and of present opinions held by students of diabetes. The mechanism of the action of insulin was introduced by Dr. Rachmiel Levine of Chicago with a description of the experiments underlying the transport hypothesis. Further studies on glucose transport and its hormonal control were presented by Park and co-workers from the Vanderbilt University School of Medicine. A series of nine papers dealt with metabolism of carbohydrates and its relation to the metabolism of fat. Special emphasis was given to hepatic metabolism as influenced by insulin and to the marked sensitivity of adipose tissue to the action of insulin. The pathoanatomy and pathophysiology of the diabetic angiopathy were presented with special reference to the lipid metabolism, the lipoprotein, the possible role of renal corticoids, and the influence of heredity. The clinical aspects of the diabetic angiopathy involving the retina, kidneys, and surgical lesions of the extremities were discussed in numerous papers.

The oral treatment of diabetes was presented from the point of view of pharmacodynamics, chemistry, and morphology. Loubatières of Montpellier, France, believed that the arylsulfonamides might have a specific effect in insulin production, an opinion shared by few writers. Data indicating that the orally given drugs produce similar physiological effects to those observed with insulin are still scanty. The hypothesis that insulin release from the pancreas is the mode of action of these drugs still lacks satisfactory proof. The effects of such drugs in juvenile patients are slight unless the child is in a period of diabetic remission.

The use of tolbutamide in 9,168 patients treated in the United States was analyzed by C. J. O'Donovan. Of these, 58% were female, less than 1% were under 20 years of age at the time of treatment, and only 5% were between 20 and 40 years of age. In contrast to the usual statement that 80% of adult diabetics are overweight, in this series 12% were asthenic, 45% were of medium build, and only 30% were heavy or obese. This figure agrees with the estimated incidence of obesity in the adult population of the United States. The body habitus is not a major determinant of response to therapy. The percentages of satisfactory control were practically identical in those patients who were of medium build and those who were obese. In this series, 14% has been on no former regimen of therapy before treatment was started with tolbutamide, since many were only recently discovered to be diabetics; 23% had been on diet alone before oral treatment; and 61.7% had had some previous insulin treatment. The highest percentages of success in treatment were in the group who had had no previous treatment with insulin.

R. H. Williams and co-workers studied not only tolbutamide and chlorpropamide but also certain biguanides, which had been shown to cause a significant decrease in hyperglycemia. Phenethylbiguanide inhibits certain oxidative enzymes. The anoxia which is produced leads to a decrease in gluconeogenesis and to an increase in the uptake of glucose by peripheral tissue. These factors lower the blood sugar level, but presumably more than these effects are required to correct the diabetic state.

Data indicating the effect of tolbutamide on various enzymatic processes in the liver were presented by Wallenfels and Creutzfeldt of Freiburg. The studies of Pfeiffer and others, demonstrating an increase in insulin output in the pancreatic vein after intravenous infusion of tolbutamide, whereas the opposite effect was obtained after injection into the femoral vein, were of special interest. Large series of patients treated with the orally given substitutes for insulin were reported by Boulin and Rambert of Paris, Marble of Boston, Bertram of Hamburg, and others.

The psychological problem encountered in the management of the severe diabetes in children were presented by Bruch of New York and Leonhardt of Karlsburg. Clinical experience stressed the difficulties of rehabilitation of severely affected children. A panel of contributors brought to the fore the problems encountered in pregnant diabetic women. Studies of adrenocortical function, the uterine blood flow, and the effects of vascular disease on the course and outcome of pregnancy in diabetics were stressed.

Methods of insulin assay were presented and the adipose tissue method of Renold was especially stressed. The determination of serum insulin levels by the rat diaphragm method gives comparable results, but apparently the more recent method, with use of adipose tissue, is more reliable. Insulin antibodies and insulin inhibitors are being studied in Cambridge, Seattle, and London. A factor in the alpha-1 globulin fraction of plasma, found in the plasma of patients with diabetic acidosis, frequently disappears after the institution of insulin therapy. It is a protein and is inactivated by chymotrypsin. In diabetic or nondiabetic subjects, after insulin injections have been given for several weeks, antibodies which inhibit the fixation of insulin to the tissues and other factors in the problem of insulin resistance were presented. The consensus of workers in the field was that intensive efforts with new techniques should add knowledge of great practical importance. This volume, replete with data, is recommended for all physicians interested in the study and treatment of diabetes.

Chemistry of Pancreatic Diseases. By Harris Busch, M.D., Ph.D., Associate Professor of Pharmacology, Department of Pharmacology, University of Illinois College of Medicine, Chicago. Publication no. 377, American Lecture Series, monograph in American Lectures in Living Chemistry. Edited by I. Newton Kugelmass, M.D., Ph.D., Sc.D. Cloth. $5.25. Pp. 160, with 22 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This book attempts to integrate the clinical, physiological, and biochemical knowledge of pancreatic diseases. This is a vast undertaking, and the author has met with varying degrees of success in his efforts. The exposition on exocrine pancreatic function is complete and excellently presented. The references to the recent applications of electron microscopy and ultracentrifugation techniques indicate the comprehensiveness of this section, but the discussion of endocrine pancreatic function is largely concerned with the details of insulin and carbohydrate metabolism and is somewhat cursory. The clinical section, particularly the part on the management of diabetes mellitus, is overly brief, and such interesting entities as the Zollinger-Ellison syndrome and hemochromatosis are not mentioned. In the concluding discussion, on neoplastic diseases of the pancreas, clinical deficiencies are evident from the omissions of the important diagnostic techniques of duodenal intubation and cytological and biochemical studies of the pancreatic fluid before and after stimulation. The material is well organized and presented clearly and the bibliography is impressive, but the inadequancies mentioned make it difficult to recommend the book wholeheartedly to the biochemist, researcher, clinician, or medical student, although each should find the volume valuable in some areas.

Gripe Asiatica. By Dr. Manoel Bruno-Lobo, in Portuguese, by the Institute of Microbiology of the University of Brazil. Rio de Janeiro, 1958, pp. 123. Price not stated.

Gripe asiática. Por Manoel Bruno-Lobo. [Trabalho apresentado em 30 de agôsto de 1958 à Comissão Julgadora do concurso "Revista Médica do IPASE" e que, merecendo o Prêmio de 1958, foi editado por essa Instituição. A parte experimental dêste trabalho foi realizada no Instituto de microbiologia da Universidade do Brasil, com a colaboração de J. Travassos, Gilda G. Bruno-Lobo e Júlia V. Vasconcellos, técnicos da Divisão de vírus, sob a orientação científica do Professor Paulo de Góes.] Paper. Pp. 123, with illustrations. Instituto de microbiologia, Universidade do Brasil, Rio de Janiero, Brazil, 1958.

This book, a prize winner in a contest sponsored by the *Medical Journal of the Institute of Pension and Retirement for State Employees*, is a study in five parts. Part 1 deals with generalities regarding Asian influenza and the role of the World Health Organization during the 1957 epidemic. Part 2 concerns the history and epidemiology of the epidemic which began in China and spread to the entire world. The disease entered Brazil through the southern border in the autumn of 1957. Part 3 deals with the laboratory investigations. Parts 4 and 5 constitute the original contributions in this work, which are the experimental, virological and serologic studies made at the Institute of Microbiology.

The material for the immunogenic study of the influenza outbreak in Rio de Janeiro, in 1957, consisted of paired serums, one in the acute and one in the convalescent phase. They came from patients at the Institute Benjamin Constant, students and recruits at the School of Aeronautics, patients at the Hospital for State Employees, private patients, and volunteer donors at the City Blood Bank. Serums were obtained also from subjects in three small communities in the state of Pernambuco, in the northeastern part of Brazil, where the epidemic had not yet spread.

The findings in each group were compared with those obtained by researchers in other parts of the world. In one of the three small communities the serum was obtained from 31 subjects prior to vaccination and 20, 35, and 50 days after vaccination. Of this sample 22% presented neutralizing antibodies for the A/Formosa-313/57 type before they were vaccinated. This is lower than the percentage of the total sample composed by the three small communities (29%) but higher than the values found by other researchers. This fact led to the hypothesis that some persons had already harbored a latent form of viral infection. Twenty days after vaccination the percentage of subjects with neutralizing antibodies reached 63%. The effectiveness of the vaccine may be evaluated in terms of the difference between the two degrees of immunization, *about 41%, which was in accordance with findings* of other researchers. There is an intensive bibliography. The book is a valuable contribution to our knowledge of Asian influenza.

Proceedings of the Research Conference on Problems of Alcohol and Alcoholism, Held at Washington, D. C., 25-26 October 1958. Sponsored by North American Association of Alcoholism Programs, under grant from National Institute of Mental Health. Proceedings editor: Ebbe Curtis Hoff. Special reprint from Quarterly Journal of Studies on Alcohol, vol. 20, no. 3, September 1959. Paper. Gratis to libraries and institutions. Pp. 415-672, with illustrations. National Institute of Mental Health, Community Services Branch, Bethesda, Md., 1959.

This book consists of 25 papers on different aspects of the problems of alcoholism. The introductory article, written by E. C. Hoff, outlines the purposes of the conference with general explanatory remarks about the proceedings. The approaches to the problem of alcoholism include the physiological, sociological, medical, psychiatric, and experimental. Biochemical and nutritional studies are also presented. Several articles describe the experiences of the staff of the Alcoholism Clinic of the New York State University College of Medicine, in Brooklyn, N. Y. Another paper is devoted to the study of alcoholics in a New England prison. Some of the reports are evaluations of drugs used in the treatment of the alcoholic patient. One paper explains the experimental use of d-lysergic acid diethylamide. Statistical reports compare the mortality among treated alcoholics and characteristics of alcoholics as related to prediction of therapeutic outcome. Comparison between alcoholics and nonalcoholics in traffic accidents is the subject of another paper.

Sociologic studies include the measuring of knowledge about alcoholism in a community, teenage drinking as group behavior, and the comprehensive approach to the problem of alcoholism. While this book can be of great value to any physician who reads it, more will be gleaned from it by the person who has had experience in the diagnosis, treatment, and general care of alcoholic patients. The general practitioner can gain much from the perusal of the sociologic papers. Some of the more technical papers dealing with the experimental approach and the biochemical studies should be of greater value to those who have specialized in the field of alcoholism. Sociologists should find many of the papers extremely interesting.

A few of the papers should be of particular interest to the clinician, since they deal with the direct contact of the physician with the alcoholic patient, but since most of these experiences are with patients in a clinic, it would be of more interest to people employed in such clinics than to private practitioners. There is, however, enough to be gained from these papers to help the private practicing physician in gaining insight into the problem of dealing with alcoholic patients. This can be of much value to him in his practice, not only in the treatment of patients who come to him suffering from the illness but also in the early detection of cases which have not become sufficiently advanced for the patient to seek help. This can be helpful in case finding. Although this book is primarily for the person who specializes in the field of alcohol and alcoholism, the nonspecialist can gain a great deal from a careful study of its contents.

1957 Inventory: Municipal and Industrial Waste Facilities. Volumes 1-9. U. S. Department of Health, Education, and Welfare, Public Health Service, Bureau of State Services, Division of Sanitary Engineering Services, Water Supply and Water Pollution Control Program, Washington, D. C. Public Health Service publication no. 622. [Cooperative state-federal report. Published by state region.] Paper. 65 cents; $1.75; $1; $1; $1.75; $1.25; $1; 60 cents; $1.25. Pp. 129; 362; 196; 160; 339; 241; 180; 109; 267. Superintendent of Documents, Govern. Print. Off., Washington 25, D. C., 1959.

These nine volumes constitute a report on community and industrial waste disposal. They consist exclusively of tables that present information about selected or specified communities, including tables for each of the states. There appears to be no attempt to obtain either city or county information which could be used to make comparisons. The format of the tables is confusing, since as many as three different items are placed in one column. For example, the first column is titled "Community, Sewer or Sanitary District, Institution or Industry," and extends across two columns of information. The next column includes the 1950 population, the 1957 estimated population, and the number of plant employees. Three entirely different items are placed in one column, making it difficult to distinguish the figures from each other in this one column or to know to what a figure refers. These volumes should prove helpful to municipal and state regulatory officials concerned with municipal and industrial waste problems and water pollution control activities.

QUESTIONS AND ANSWERS

MIGRAINE HEADACHES

To the Editor:—*A 48-year-old patient has suffered from headaches since he was 21 years old. He has been seen by numerous doctors and consultants, and the diagnosis consistently has been histamine-type headache, localizing in the right temporal blood vessels. He is confused by a variety of statements concerning the efficacy or uselessness of the following procedures (some of which have been tried): (1) desensitization with intravenously given histamine, (2) treatment by subcutaneous administration of a histamine-azoprotein complex, (3) treatment with repeated small doses of x-ray (apparently based on the same principles as treatment of postherpetic neuralgia), and (4) a number of ancillary and nonspecific types of therapy. What are the therapeutic potentialities of one or more of the three procedures enumerated?*

T. H. Klunder, M.D., Hatch, N. Mex.

Answer.—Paroxysmal attacks of cluster headaches have been well documented during the past 90 years under a variety of clinical entities and eponyms. Most theories state that they are periodic episodes of local dilatation in extracranial vessels, mainly those supplied by the branches of the external carotid arteries (i.e., migraine).

The subcutaneous and intravenous administration of histamine has been recommended by Horton (for suggested dosage and plan of histamine therapy see Horton, B. T.: Histaminic Cephalgia, Horton's Headache or Syndrome: Provocative Tests, *Triangle* 3:66 [June] 1957) and recently he has advocated the use of whole cortical extract, ACTH, or cortisone (100 mg. intravenously daily), three or four days or longer before desensitization. Most clinicians who have experience with this syndrome have found histamine quite ineffective. There is no adequate prophylactic treatment other than reduction of stress factors. The intensity of the attacks can be modified with nonspecific chemotherapy, nonspecific medical attention, resolution of personal problems, emotional support, and rest. Ergotamine tartrate is effective for relief of symptoms.

OXYGEN FOR ATHLETES

To the Editor:—*Of what value is oxygen in relieving the dyspnea caused in athletes by physical exertion? Would administration of oxygen restore strength to an exhausted athlete?*

A. C. Scott, M.D., Stillwater, Okla.

Answer.—The present fad of administering oxygen to hasten recovery of athletes after physical exertion is not based on sound principles of physiology. Experimental evidence on the subject is conflicting, and, because of the effects of practice and warmup periods, studies are difficult to control. The body does not store up oxygen, and, since the effect of oxygen-inhalation wears off in about three minutes, no benefits can be anticipated from administration of oxygen in activities involving prolonged exertion. Inhalation of oxygen by athletes immediately before participation in events such as short track sprints and short swimming races (in which breath-holding is a factor) may be of limited value, but these benefits probably can be obtained in the same degree by forced deep-breathing of ordinary air.

A review of scientific studies on the influence of oxygen administration to athletes was carried out in 1953, and the Joint Committee on Health Problems in Education of the National Education Association and the American Medical Association concluded: "Valid scientific evidence in support of the value of administration of oxygen in athletic competition is lacking. It is unwise and dangerous to encourage the athlete to exert himself beyond the limits he has learned to respect from instinct and experience. The anticipation of help from oxygen inhalations increases this possibility. The Joint Committee therefore strongly recommends that the use of oxygen for such purposes be disapproved." In 1955, the Committee reviewed the above statement and reaffirmed its stand.

CONTROL OF CEREBRAL EDEMA

To the Editor:—*What treatment will reduce the intracranial edema in a patient with concussion or fracture of the skull who does not have any signs and symptoms of intracranial pressure due to localized hematoma?*

M.D., New York.

Answer.—The localized areas of cerebral edema which occur after trauma to the head are believed to be due to the increased permeability of capillaries. In most patients this condition is reversible and clears in a few days, but in children it can

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

progress to liquefaction necrosis and may cause death. A localized area of this type of edema is, in its relation to the brain, an intracerebral mass. Therefore, its appearance may simulate contusion, hematoma, abscess, or neoplasm in a pneumoventriculogram or cerebral angiogram.

Theoretically, the intravenous administration of hypertonic solutions, if given early in the treatment, should decrease cerebral edema. At present urea is the preferred agent. Although the use of all such solutions carries the risk of secondary increase in cerebral edema when the solute leaves the blood stream through damaged capillaries and enters the swollen cerebral tissue, urea minimizes this hazard, and its use is, therefore, definitely helpful immediately before craniotomy.

Another major risk of systemic dehydration is the presence in the patient of unrecognized intracranial hemorrhage; such areas of hemorrhage may increase with the relative decrease of brain volume. Systemic dehydration may also cause or prolong fever.

The head and chest of patients with traumatic cerebral edema should be elevated to lower intracranial venous pressure. Adequate respiratory function, total protein content, electrolyte and water balance, and hemoglobin level of the blood must be maintained in the patient. Mercurial diuretics, chlorothiazide and its derivatives, acetazolamide, and steroids have not been established as beneficial therapeutic agents for the management of patients with traumatic cerebral edema.

WRITING PROBLEMS OF LEFT-HANDED CHILDREN

To THE EDITOR:—*A 5-year-old girl who is left-handed writes from right to left and also produces an upside-down mirror image. I would appreciate suggestions about the diagnosis and treatment of this patient.*

John M. Bell, M.D., Marinette, Wis.

ANSWER.—When a child is naturally left-handed, his speech center usually develops in the opposite cerebral hemisphere, in conformity with the economy or symmetry of cerebral organization. An attempt to force the child to change the hand used in writing may lead to functional confusion in the brain and an attempt to switch the speech center, which may result in a stammer.

Images of objects observed by the right part of the visual field are transmitted by the lens to the left side of each retina. The impulses go from the retina through the left optic tract to the left visual cortex, where they easily transfer to the left brain center, i. e., to the site of origin of impulses for reflex protective movements of the right arm.

The mental image of objects in the right visual field is related to the right hand and to the right eye, and the act of writing is a hand movement directed toward the right visual field and best seen by the right eye. The left-handed child's attempt to write makes him move the pencil toward the left side and upside down. (Orton: *A. M. A. Arch. Opth.* 30:707 [Dec.] 1943). Adults with right homonymous hemianopsia have to read into a blind area, which is difficult even when they have 20/20 vision. Some of them find it easier to read upside down, in which case they read toward the seeing part of the visual field.

A child should be urged gently to change from left-handedness to right-handedness; if he stubbornly refuses to do so, special teaching procedures must be applied to correct his mirror writing and reading.

HIGH FREQUENCY SOUNDS

To THE EDITOR:—*Where can I obtain information that would relate the deleterious effect of high-pitched sounds on rats to the pathogenesis of convulsive seizures that are caused by such sounds?* *Vito Vighi, M.D., Ottawa, Ill.*

ANSWER.—Because of anatomic differences in the various animals used for such experiments, nearly all recent histopathological studies on "acoustic injury" to the ear have been performed on guinea pigs and, apparently, none on rats (Davis: *Physiol. Rev.* 37:1 [Jan.] 1957; on submicroscopic damage, see Spoendlin: *Pract. oto-rhino-laryng.* 20:197 [July-Sept.] 1958). The highest pitch used in these experiments with guinea pigs was about 6,000 cps, which is high pitch for man but not for the rat. The most audible pitch for rats is apparently about 40,000 cps (Gould and Morgan, *Science* 94:168 [Aug. 15] 1941, and the rat produces sounds composed of up to at least 80,000 cps (Anderson, *Science* 119:808 [June 4] 1955).

VERTIGO AND AURICULAR FIBRILLATION IN THE GERIATRIC PATIENT

To THE EDITOR:—*What is the treatment for elderly patients who (1) faint when they make a sudden change in posture and (2) have auricular fibrillation?* *M.D., Pennsylvania.*

ANSWER.—Positional "dizziness" is a frequent complaint of elderly persons and is considered an accompaniment of cerebral atherosclerosis due to the inability of the cerebral circulation to adapt quickly enough to a change in position. Vertigo is precipitated by the movement of the body and not its changed position.

Elderly persons are disabled by many pathological processes which contribute to inefficient responses of the body. Treatment is directed toward a decrease in the severity of the patient's symptoms and the best possible restoration of his health. Despite the manufacturers' claims of their therapeutic efficacy, new antimotion drugs have little effect on this type of vertigo. Ephedrine, 25 to 50 mg. taken three times daily, seems to be most effective in decreasing the frequency and severity of the faintness. The patient should be instructed not to move suddenly, and the physician must continue to reassure the patient that the difficulty is not serious.

Rapid auricular fibrillation must be controlled with administration of digitalis or a digitalis-like drug. Elderly patients who develop a slow auricular fibrillation that progresses slowly do not require digitalis therapy. Many physicians feel that conversion to a normal sinus rhythm should be attempted, while others are satisfied with a controlled rate, with or without administration of digitalis. Generally, patients with controlled fibrillation in the age group described who feel and do well need not be treated. Patients who are disturbed by the palpitations and thus are difficult to control, or who are heart-conscious and whose heart rhythm is easily converted and maintained, should be treated, however.

TEST FOR POISONOUS MUSHROOMS

To the Editor:—*Some persons who think they can tell nonpoisonous from poisonous mushrooms have asked if there is some simple chemical test that can be used to indicate the difference. Is there any such test?*

Joseph L. Mangiardi, M.D., Garden City, N. Y.

Answer.—Analytic methods for the detection and quantitative estimation of one of the toxic principles (muscarine) in mushrooms are available. The practical use of these methods is limited by their complexity, and, more important, the varieties of toxic mushrooms contain different toxic principles. There is no simple test which will detect all of the poisonous principles which may be found in mushrooms.

CERVICAL JOINT STRAIN

To the Editor:—*A 36-year-old man, whose automobile was struck from behind, suffered acute muscle strain of the cervical vertebral joints. Three days later he noted a hearing loss, and audiometric tests showed that he had a 20-db hearing loss in the low tones and one of 40 db in the high tones in each ear. Could there be any relationship between acute cervical joint strain and hearing loss?*

Ephraim L. Manning, M.D., Davenport, Iowa.

Answer.—It is extremely difficult to answer this question with the incomplete amount of information given. We do not know what this patient's hearing by bone conduction is, but, in general, this hearing loss suggests a bilateral perceptive deafness of slight degree. If this were due to a hydrops of both cochlear labyrinths, adequate treatment for this disease should cause some change in the audiometric picture, since the degree of deafness is slight, but it is unlikely that the involvement would be bilateral. A bilateral perceptive deafness of equal degree involving both cochlear nerves would not have any relation to the type of injury this patient sustained.

PARENTAL CONSENT

To the Editor:—*We have a difference of opinion about the necessity of parental permission for the performance of a pelvic examination on a young girl. The nurses at two colleges in this community have been told that no patient under 21 years of age should have a pelvic examination without written permission from her parents. The administrative policy in the two colleges is to refer a girl with a pelvic complaint to us for discussion and evaluation of her problem and, if an examination is needed, to obtain the parents' permission by letter or telephone. This seems a waste of time and money, and it is my impression that 18 years is the legal age of consent for women in Illinois.*

Mary Louise Newman, M.D., Jacksonville, Ill.

Answer.—Young girls attain legal adult status at the age of 18 years in Illinois. A girl mature enough to attend college is considered able to make her own decision about having a pelvic examination, even though she may be under 18 years of age. The physician should not hesitate to perform the examination if a teen-ager has profuse bleeding, severe abdominal pain, or other signs of symptoms which require investigation and treatment. If a college girl consents to a pelvic examination, it can be performed, when necessary, to ascertain that her pelvic organs are normal. If a vaginal examination appears to be too uncomfortable for the patient, a rectal examination often will suffice. It is important that a male physician remember to have his nurse or secretary in the room during the course of the examination.

TRANSAMINASE TEST

To the Editor:—*If serum transaminase levels are used as a prognostic criterion, when should a patient convalescing from viral hepatitis be allowed to be ambulant?*

William E. Arbuckle, M.D., Indianapolis.

Answer.—The serum glutamic oxalacetic transaminase (SGO-T) level is one of the best quantitative measures of acute liver injury, but it must be remembered that, when liver failure develops (with precoma or coma), the levels usually fall. The test provides a fair index of the patient's ability to commence or increase ambulation, but individual variations preclude the possibility of setting up standard levels. Excessive exertion by the patient can cause a sharp rise in his transaminase level; therefore, it cannot be stated whether this test would be more significant than others. If results of liver function tests show deterioration of the patient's condition with a given amount of physical exertion, it is probable that the inflammatory reaction in the liver has increased. The transaminase level should be below 100 units before the patient is allowed unrestricted ambulation.

FACIAL MUSCLE TIC

To the Editor:—*A 62-year-old man has a tic of the muscles of expression on the right side of his face. He has had it since 1941, and it has gradually become worse. The tic is most noticeable and severe when the patient suffers emotional stress. He has consulted a neurosurgeon who, because the patient has poor vision in the left eye, advised against alcohol injections to interrupt the nervous pathways of the tic. Interruption of the nerve tracts might interfere with the blink reflex in the right eye, which would diminish the total visual acuity. Since the center of his tic is in the musculature of expression around the zygomatic arch, or somewhat below, and spreads superiorly and inferiorly to involve the platysma on that side, would an alcohol injection of the maxillary branch only of the trigeminal nerve be of benefit to this patient? Past medical therapy has consisted of general sedation with barbiturates, tranquilizers, mephenesin, nicotinic acid, thiamine hydrochloride, vitamin B_{12}, and procaine hydrochloride infusion to the trigger point of the tic. None of these measures has been successful.*

George M. Wolverton, M.D., Clarksville, Ind.

Answer.—The problem of the patient who is suffering from a right facial tic is fraught with therapeutic difficulties. The right seventh nerve is affected, and alcohol injection is both technically difficult and contraindicated because of poor vision in the right eye. Since the patient has had neurosurgical consultation, it would be best not to attempt further treatment.

EYE IRRITATIONS AND ANESTHETIC AGENTS

To the Editor:—*As an anesthesiologist I am concerned with the complication called "ether eye" after administration of ether anesthesia. Information about the prognosis of patients with this complaint will be appreciated.*

Stephen H. Mazur, M.D., Maplewood, N. J.

Answer.—Ether eye is a keratoconjunctivitis or simple conjunctivitis that occurs in a patient after the administration of open-drop ether anesthesia, during which liquid ether may or may not have come into contact with the eye. It is usually a self-limiting condition which seldom requires treatment other than application of an anesthetic ophthalmic ointment, such as tetracaine hydrochloride, for the local relief of pain. The patient's eye should be covered with a patch, in the more severe cases. Permanent sequelae, such as corneal opacities or iritis, occasionally occur; when they do, the etiological question is whether or not additional trauma to the eye occurred during administration of the anesthesia or during the postoperative recovery of the patient. If ether vapor is used as the anesthetic agent, a generalized vasodilation of blood vessels in the conjunctival membranes can occur.

TREATMENT OF BURSITIS

To the Editor:—*Is there a therapeutic agent, administered by hypodermic injection, that will cure a patient of an olecranon bursitis?*

William S. Levy, M.D., Woonsocket, R. I.

Answer.—Intrainjection of hydrocortisone, or similar derivatives, has proved of considerable value in relieving olecranon bursitis, with or without a collection of fluid, in most patients. One method is to dilute 1 to 1.5 cc. (25 mg. per cubic centimeter) of hydrocortisone in 4 or 5 cc. of a local anesthetic and inject the mixture into the bursal space after as much as possible of the bursal fluid has been drained. It usually is wise to apply pressure by means of a rubber sponge and an Ace bandage for a period of two or three days. This procedure can be repeated in one to two weeks, if necessary. For the patient with a severe chronic olecranon bursitis this procedure may not be adequate and surgical excision of the bursa may have to be performed.

REMOVAL OF SUPERNUMERARY BREAST

To the Editor:—*Should supernumerary mammary glands be excised as a preventive measure against development of a breast cancer?*

La Salle Mondor, M.D.,
Grand 'Mere, Quebec, Canada.

Answer.—Supernumerary mammary glands, a form of polymastia, occur frequently in women and may be associated with polythelia, or supernumerary nipples, which are usually located along the milk line on one side or both sides. The prophylactic removal of supernumerary mammary glands is not indicated unless the presence of a tumor can be demonstrated. The glands in the breast may be affected by the menstrual cycle and may cause swelling and tenderness, which usually regresses after menstruation, in the axilla. There is no more reason to remove such tissue as a prophylaxis against cancer than there is to remove normal mammary glands.

WASHINGTON NEWS

Chemical Additives Review . .
Deaths from Influenza Increase . .
A. M. A. on Pilot Physicals . .
Administration vs. White Fleet . .
Hearings on Automobile Exhaust . .

PRESIDENT DIRECTS STUDY OF ADDITIVES

President Eisenhower ordered three federal agencies to make reports to him on the use of chemical additives in food, an issue that has stirred considerable controversy since last autumn when the government banned some lots of cranberries.

In handing down the order, the White House made clear that the study "has no relation to the enforcement of the appropriate laws" by the Department of Health, Education, and Welfare. "These laws were enacted for the protection of the consumers of the nation and will continue to be strictly enforced," the statement said.

The Food and Drug Administration, the Agriculture Department, and President Eisenhower's Science Advisory Committee were assigned to report on the subject of chemical additives that are used to store, flavor, and color foods.

President Eisenhower, according to White House Press Secretary James Hagerty, "wants to find out the various problems in the whole field and asked these scientists to make this investigation."

HEW Secretary Arthur S. Flemming said that he had no intention of suspending enforcement of the chemical additives laws pending results of the study.

The study should be completed in the near future, said Hagerty. The administration has asked Congress to modify present statutes to allow tolerances on color additives that may cause injury when fed in large quantities to test animals but which would not be harmful in minute amounts. Under present law, tolerances are not allowed. However, the administration has urged retention in the color bill of a ban against tolerances for chemical additives that cause cancer.

The latter recommendation has drawn the fire of the pharmaceutical industry which contends it is too rigid. In testimony before the House Commerce Committee, Dr. Thomas P. Carney, testifying for the Pharmaceutical Manufacturers Association, said he did not believe that it was the intent of Congress to prevent the use of any chemicals that "would be safe when used in regulated amounts and under proper conditions."

Mr Flemming, however, has announced that he will ask Congress to relax the anticancer provision of the law so as to allow the use of additives that may cause cancer in test animals provided there is no residual amount of the material in the food as eaten by consumers. This would permit continued use of the hormone-like chemical stilbestrol in feed for beef cattle.

DEATHS FROM INFLUENZA AND PNEUMONIA RISE

The Public Health Service reported sharp increases in deaths from influenza and pneumonia. During the first five weeks of this year, 4,033 such deaths were reported by the 108 large cities that supply weekly death data to the government. The total was a 44% increase from the 2,798 deaths for the same period in 1959 and a 20% increase from the 3,357 reported in the same period of 1958.

Deaths from all causes in large cities this year are also more numerous than they were during the same period of the two previous years, PHS said.

Commenting on the high number of deaths from influenza and pneumonia, Dr. Burney said,

"The figures seem to bear out clinical impressions of some physicians that they are encountering a more than normal amount of pneumonia this year. Reports from some areas that absenteeism is higher in industrial populations than in school populations, as well as some reports that the majority of pneumonia and influenza deaths are occurring in the over-65 age group, suggest that the respiratory infections this year are attacking adults more frequently than children."

Almost half of the states confirmed the diagnosis of Asian-type influenza in one or more areas, but their reports showed a pattern of localized outbreaks rather than the progressive and complete involvement of wide areas that characterized the 1957-58 Asian influenza epidemic.

After outbreaks occur, vaccination cannot be expected to have much value in controlling influenza, according to Dr. Burney. "However, with proper medical and nursing care, many of its serious complications can be avoided," he said.

A. M. A. BACKS DESIGNATED PHYSICIANS FOR PILOT CHECKS

The American Medical Association urged the Federal Aviation Agency to require that only specially designated physicians be allowed to examine private and student pilots for license qualifications. Testifying at an agency hearing on this proposal, Dr. Hugh H. Hussey, member of the A. M. A.'s Board of Trustees, noted that the A. M. A House of Delegates has approved a resolution stating, in part, "These examinations should be made by those physicians who are qualified to make aeronautical-type examinations, so that the best interests of the public, and especially of those who operate or utilize aircraft, may be served."

(Continued on page 26)

"In order that the mental and physical fitness of an air crew member may be safely determined, the examiner must be a doctor of medicine with special knowledge and proficiency in certain techniques," according to the report made to the House of Delegates.

At present, designated medical examiners are required for physical examinations of commercial pilots. The FAA has proposed extending this to all pilots.

Asked if the A. M. A.'s position ran counter to the principle of free choice of physician, Dr. Hussey replied, "Let me assure you that the A. M. A. still jealously guards the principle of freedom of choice where this refers to medical care in the broad sense. The type of examination that we are talking about here is not really in the area of medical care generally. This would be analogous in some respects to the activities of a health officer, for example."

Supporting the A. M. A.'s stand was Dr. Neal Baxter, president of the Civil Aviation Medical Association, who declared that even a well-trained physician could not be expected to assess pilots' physical qualifications without specific instruction.

A spokesman for the Flying Physicians' Association criticized some aspects of the proposal but indicated the organization supported the principle.

Dr. Malcolm Phelps of the American Academy of General Practice took issue with the proposal, declaring that family physicians are more familiar with their patients and better qualified to examine persons whose case histories are familiar.

Also opposing the plan were representatives of the Aircraft Owners and Pilots Association, National Pilots Association, and Utility Airplane Council of Aerospace.

However, Dr. Ludwig Lederer of Aerospace Medical Association said the proposal would not interfere with the principle of free choice of physician and recommended that the number of qualified examiners be increased.

The FFA proposal is part of a wide new safety program instituted by the new federal agency. A Senate aviation subcommittee headed by Sen. Mike Monroney (D., Okla.) has been holding hearings on the new rules and the general subject of air safety.

ADMINISTRATION OPPOSES DISASTER RELIEF FLEET

The administration told Congress that the proposal for a "great white fleet" of naval vessels to bring medical and other relief to foreign countries "does not appear to be practical."

In a letter to the House Armed Services Committee, the Navy Department said its "experience in disaster relief is that one small group of ships could not be expected to render timely and effective aid in any significant number of natural disasters."

Proposals for a great white fleet have been introduced by many lawmakers since last year. Under them, surplus naval vessels would be restored to working order and would tour the world furnishing food and medical assistance to nations needing them.

The Navy said the concept was "laudable," but that it would "not warrant the large expenditures of funds which would be required." As now established, with bases spread around the globe, the Navy is in a good position to render emergency relief without setting up a separate fleet, according to the letter.

Project Hope, the soon-to-be dispatched hospital ship financed by private funds, may be used as an aid in determining the potential value of a great white fleet, said the Navy, in the letter that was cleared by the budget bureau.

The administration's position appeared to weigh heavily against chances of Congress passing such legislation this year.

HEARINGS ON AUTOMOBILE EXHAUST SLATED

A House commerce subcommittee scheduled hearings on air pollution, as two lawmakers called for installation of smog filters on all automobiles. Subcommittee Chairman Kenneth Roberts (D., Ala.) called public health officers and automobile industry spokesmen to testify. He said that automobile-caused air pollution is a problem of all metropolitan areas.

Meanwhile, Sen. Wayne Morse (D., Ore.) contended that auto makers could install exhaust devices for less than $1 a car, and he urged that they be made standard equipment. Representative Roberts said this was one of the major questions he would put to the industry witnesses.

MISCELLANY

The Senate passed and sent to the White House legislation almost doubling federal funds for combating water pollution. The bill would increase to 900 million dollars the present 500-million-dollar ceiling on federal grants to states and localities for construction of sewage plants and other steps to reduce water pollution. The authorization is over a 10-year period. The administration had urged a cutback in the federal share of the program on the grounds that it is largely a community responsibility.

A House veterans' affairs subcommittee held one week of hearings on the adequacy of funds to provide for maintenance, repair, and construction of Veterans Administration facilities. Directors of VA hospitals and spokesmen for veterans' organizations were the principal witnesses. Many urged increases in appropriations. The hearing was part of the subcommittee's annual review of such matters.

A House judiciary subcommittee planned hearings in March on various proposals for a White House Conference on Narcotics.

The Children's Bureau of the Social Security Administration issued a new pamphlet to encourage and instruct parents of children handicapped by the absence of an arm or leg. The document, "The Child with a Missing Arm or Leg," may be obtained from the Superintendent of Documents, Government Printing Office, Washington 25, D. C., for 25 cents a copy.

The 350-bed Public Health Service Hospital for tuberculosis patients at Manhattan Beach, Brooklyn, N. Y., will be closed June 15 because of the decreasing number of patients.

"SUNNY SIDE UP"

Specific effectiveness
in morning sickness
with

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- **Prevention of nausea and vomiting**
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Mornidine (brand of pipamazine), another achievement of Searle Research, provides selective action on the vomiting center with very little drowsiness. Mornidine is extremely effective in morning sickness. In 145 pregnant patients, 91 per cent had "excellent" or "good" relief from nausea and vomiting.

Doses of 5 mg. at intervals of six to eight hours provide effective relief all day. Suggestion: first tablet to be taken upon awakening.

For patients unable to retain oral medication when first seen, Mornidine may be administered intramuscularly in doses of 5 mg. (1 cc.).

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MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., *Chicago 10, Executive Vice-President.*

1960 Annual Meeting, Miami Beach, Fla., June 13-17.

1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 2.

1961 Annual Meeting, New York City, June 26-30.

1961 Clinical Meeting, Denver, Nov. 27-Dec. 1.

1962 Annual Meeting, Chicago, June 11-15.

1962 Clinical Meeting, Los Angeles, Nov. 25-30.

AMERICAN

1960

February

American College of Allergists, Inc., Americana Hotel, Bal Harbour, Miami Beach, Fla., Feb. 28-Mar. 5. Mr. Eloi Bauers, 2160 Rand Tower, Minneapolis 2, Executive Vice-President.

American College of Surgeons, North Carolina Chapter, Hotel Barringer, Charlotte, N. C., Feb. 26-27. For information write: Dr. Alexander Webb Jr., 201 Bryan Bldg., Cameron Village, Raleigh, N. C.

American College of Surgeons, Sectional Meeting for Surgeons and Nurses, *Statler Hilton, Boston,* Feb. 29-Mar. 3. For *information* write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Orthopsychiatric Association, Inc., *Sherman Hotel,* Chicago, Feb. 25-27. Marion F. Langer, Ph.D., 1790 Broadway, New York 19, Executive Secretary.

Symposium on Fundamental Cancer Research (14th), University of Texas, Houston, Feb. 25-27. For information write: University of Texas M. D. *Anderson Hospital & Tumor Institute, Houston* 25, *Texas.*

March

American Broncho-Esophagological Association, Deauville Hotel, Miami Beach, Fla., Mar. 15-16. Dr. F. Johnson Putney, 1712 Locust St., Philadelphia 3, Secretary.

American Academy of Forensic Sciences, Drake Hotel, Chicago, Mar. 3-5. Dr. W. J. R. Camp, 1853 W. Polk St., Chicago 12, Secretary-Treasurer.

American Academy of General Practice, Philadelphia, Mar. 18-24. Mr. Mac F. Cahal, Volker Blvd., at Brookside, Kansas City 12, Mo., Executive Director.

American Association for the History of Medicine, Inc., Charleston, S. C., Mar. 24-26. John B. Blake, Ph.D., c/o Smithsonian Institution, Washington 25, D. C., Secretary.

American College of Surgeons, *Sectional Meeting,* The Broadmoor, Colorado Springs, Colo., Mar. 21-23. For *information write:* Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, *Sectional Meeting,* Sheraton-Portland Hotel, Portland, Ore., Mar. 28-30. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Gastroenterological Association, Roosevelt Hotel, New *Orleans,* Mar. 31-Apr. 2. Dr. Wade Volwiler, Dept. of Med., Univ. of Washington, Seattle, Secretary.

American Gastroscopic Society, *Roosevelt Hotel, New Orleans,* Mar. 30. Dr. Arthur M. Olsen, Mayo Clinic, Rochester, Minn., Secretary-Treasurer.

American Laryngological Association, Deauville Hotel, Miami Beach, Fla., Mar. 18-19. Dr. Lyman Richards, Massachusetts Institute of Technology, Cambridge 39, Mass., Secretary.

American Laryngological, Rhinological and Otological Society, Inc., Deauville Hotel, Miami Beach, Fla., Mar. 15-17. Dr. C. Stewart *Nash, 708 Medical Arts Bldg., Rochester* 7, N. Y., *Secretary.*

American Otological Society, Deauville Hotel, Miami Beach, Fla., Mar. 13-14. *Dr. Lawrence R. Boies, University Hospital, Minneapolis* 14, Minn., Executive Secretary-Treasurer.

American Otorhinologic Society for Plastic Surgery, Inc., Deauville Hotel, Miami Beach, Fla., Mar. 6-13. Dr. Joseph G. Gilbert, 75 Barberry Lane, Roslyn Heights, N. Y., Secretary.

American Psychosomatic Society, *Sheraton-Mount Royal Hotel,* Montreal, Mar. 26-27. Miss Joan K. Erpf, 265 Nassau Rd., Roosevelt, N. Y., Executive Assistant.

American Radium Society, Caribe Hilton Hotel, San Juan, Puerto Rico, Mar. 17-19. Dr. Robert L. Brown, Robert Winship Clinic, Emory University, Atlanta 22, Ga., Secretary.

Association of Clinical Scientists, DeWitt Clinton Hotel, Albany, N. Y., *March 3-5. Dr. Robert P. MacFate, 54 W. Hubbard St., Chicago* 10, Secretary.

Intermountain Pediatric Society, *Stardust Hotel, Las Vegas, Nev.,* Mar. 28-29. *Dr. Joseph R. Newton,* 2000 S. 9th East, Salt Lake City, Utah, Publicity Chairman.

Missouri State Medical Association, Sheraton-Jefferson Hotel, St. Louis, Mar. 13-16. Mr. T. R. O'Brien, 634 N. Grand Blvd., St. Louis 3, Executive *Secretary.*

National Health Council, National Health Forum, Miami, Fla., Mar. 13-18. Mr. *Philip E. Ryan, 1790 Broadway, New York* 19, Executive Director.

National Multiple Sclerosis Society, New York City, Mar. 8. Mr. Donald Vail, 257 Fourth Ave., New York 10, Secretary.

Neurosurgical Society of America, Del Monte Lodge, Calif., Mar. 30-Apr. 2. Dr. Raymond K. Thompson, 803 Cathedral St., Baltimore 1, Secretary.

New Orleans Graduate Medical Assembly, *Roosevelt Hotel,* New Orleans, Mar. 7-10. Miss Irma B. Sherwood, 1430 *Tulane Ave.,* New Orleans 12, Executive *Secretary.*

Southeastern Surgical Congress, Roosevelt Hotel, New Orleans, 21-24. Dr. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga., Exe Secretary.

Southwestern Society for Nuclear Medicine, Menger Hotel, Sa tonio, Texas, Mar. 26-27. Dr. N. T. *Werthessen, Southwest* Foun for Research and Education, R. R. 4, *Box* 86, San Antonio 7, T *Program* Chairman.

Southwestern Surgical Congress, Riviera Hotel, Las Vegas, Nev., 28-31. Miss Mary O'Leary, 1213 Medical Arts Bldg., Oklahoma Okla., Executive Secretary.

April

Alabama, Medical Association of the State of, Admiral Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackso Montgomery 4, Executive Secretary.

American Academy of Neurology, Eden Roc Hotel, Miami, Fla. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Exe Secretary.

American Association for the Advancement of Science, Secti Medical Sciences, *Vanderbilt University, Apr. 18-19.* Dr. Geo Meneely, Vanderbilt University School of Medicine, Nashville 5, Chairman.

American Association of Anatomists, *Statler-Hilton,* New York Apr. 11-16. Dr. Louis B. Flexner, Dept. of Anatomy, School of Me Univ. of Pa., Philadelphia 4, *Secretary-Treasurer.*

American Association of Immunologists, Chicago, Apr. 11-1 *Calderon Howe, Columbia Univ. College of Physicians* and Su New Yorl [illegible]

American [illegible] and Bacteriologists, Peabody, [illegible] Dr. Russell L. Holman, of Pathology, L. S. U. School of Medicine, New Orleans, La.,

American Association of Railway Surgeons, Drake Hotel, C Apr. 7-9. Mr. Chester C. Guy, 5800 Stony Island Ave., Chica *Executive Secretary.*

American College Health Association, Toronto, Canada, Apr. *Dr. Norman S.* Moore, Cornell University, Gannett Clinic, Ithaca, Secretary-Treasurer.

American College of Obstetricians and Gynecologists, Neth Hilton Hotel, *Cincinnati, Apr. 2-6. Mr. Donald F. Richardson,* Monroe St., Chicago 3, Executive Secretary.

American College of Physicians, Mark Hopkins & Fairmont, San cisco, Apr. 4-9. Mr. E. R. Loveland, 4200 Pine St., Philadelp Executive Secretary.

American College of Surgeons, *Sectional* Meeting, Hotel Leam Minneapolis, Apr. 11-13. For information write: Dr. H. P. Sa 40 E. Erie St., Chicago 11.

American College of Surgeons, *Sectional* Meeting, Kahler Rochester, Minn., Apr. 14. *For information write:* Dr. H. P. Sa 40 E. Erie St., Chicago 11.

American College of Surgeons, *West Virginia Chapter,* The brier, White Sulphur Springs, W. Va., Apr. 1-2. Dr. Ray E. Grace Hospital, Welch, W. Va., Vice-President.

American Dermatological Association, Inc., Boca Raton Hote Raton, Fla., Apr. 8-12. Dr. Wiley M. Sams, 308 Ingraham Bldg., 32, Fla., Secretary.

American Physiological Society, Chicago, Apr. 11-15. Ray G. *D.Sc., 9650 Wisconsin Ave., Washington 14, D. C., Executive* Se

American Proctologic Society, Shamrock Hilton Hotel, Houston, *Apr. 25-27. Dr. Norman D. Nigro,* 10 Peterboro, *Detroit 1,* Se

American Public Health Association, Southern Branch, M Tenn., Apr. 13-15. Dr. L. M. Graves, Shelby County Health ment, Memphis, Tenn., Chairman, Local Arrangements Comm

American Society for Artificial Internal Organs, Pick-C Hotel, Chicago, Apr. 10-11. *Dr. Charles K. Kirby, 3400* Spr Philadelphia 4.

American Society of Biological Chemists, Inc., Chicago, Apr. Dr. Frank W. Putnam, Dept. of Biochemistry, Univ. of Florida, ville, Secretary.

American Society for Experimental Pathology, Pick-Congress Chicago, Apr. 11-15. Dr. J. F. A. McManus, Univ. of Alabam Center, Birmingham, Ala., Executive Secretary.

American Society of Facial Plastic Surgery, Hotel *Elysee,* Ne City, Apr. 6. Dr. *Samuel* M. Bloom, 123 E. 83d St., New Yo Secretary.

American *Society of Internal Medicine, Sheraton-Palace* Hote Francisco, Apr. 1-3. Mr. Robert L. Richards, 350 Post St., San Fr 8, *Executive Director.*

American Society for Pharmacology and Experimental T peutics, Inc., Chicago, Apr. Dr. Karl H. Beyer Jr., Merck Sha Dohme Research Labs., West Point, Pa., Secretary.

American Society for the Study of Sterility, Sheraton-Gibson *Cincinnati, Apr. 1-3. Dr. Herbert H. Thomas, 920 S.* 19th St., ham 5, Ala., Executive Secretary,

American Surgical Association, The Greenbrier, White Sulphur W. Va., Apr. 3-6. Dr. W. A. Altemeier, Cincinnati General Ho Cincinnati 29, Secretary.

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Arkansas Medical Society, Pine Bluff, Apr. 18-20. Mr. Paul C. Sch 218 Kelley Bldg., Fort Smith, Ark., Executive Secretary.

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Florida Medical Association, Robert Meyer Hotel, Jacksonville, 8-12. Mr. W. Harold Parham, 735 Riverside Ave., Jacksonville 3, Executive Director.

Harvey Cushing Society, Fairmont Hotel, San Francisco, Apr. 1 Dr. Edmond J. Morrisey, 450 Sutter St., San Francisco, Chairm

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NEUROSURGICAL TREATMENT OF SPONTANEOUS INTRACRANIAL HEMORRHAGE

IMPORTANCE OF DIFFERENTIAL DIAGNOSIS IN "CEREBRAL APOPLEXY" AND EVALUATION OF LONG-TERM POSTOPERATIVE RESULTS

Michael Scott, M.D., Philadelphia

The appropriateness of anticoagulants in treatment of real or apparent cerebral apoplexy depends on the differential diagnosis between hemorrhage and occlusion. Because recent animal experiments show that anticoagulants increase bleeding into infarcts produced by occluding blood vessels, the author questions the use of anticoagulants in any primary cerebral vascular accident. A follow-up study was made in 30 patients in whom certain indications had led to exploratory trephination and ultimately to verification of the diagnosis of hemorrhage. In two patients the hemorrhage was into a tumor. Nine others died in the hospital, and 19 who were discharged from the hospital after operation were available for follow-up study. The history of a hypertensive woman aged 25 years is given in detail to illustrate the clinical course of a hemorrhage into the internal capsule and the resumption of occupational activity after operation despite residual paralyses. Hemorrhages into the internal capsule were more serious than hemorrhages into the temporal lobe, but in both situations lives were saved by prompt neurosurgical intervention.

CEREBROVASCULAR disease is the third most common cause of death in the United States. In 1956 there were 177,845 reported deaths from vascular diseases of the central nervous system.[1] This is over four times the number of persons that died from motor vehicle accidents and six times the death rate from diabetes during that year.[1] It is estimated that there are over 1,800,000 victims of cerebrovascular disease in the United States today.[2]

The justified pessimism which existed 20 years ago concerning the success of medical or surgical therapy in cerebrovascular disease has been modified during the past 10 years by reports of an increasing number of patients whose lives have been saved and in whom neurological disability has been lessened by more accurate diagnosis, selective medical and neurosurgical therapy, and use of rehabilitation measures. The relatively recent acceptance of cerebral angiography as an important aid in the differential diagnosis of "stroke problems" has revealed an unsuspected incidence of congenital cerebral berry aneurysms, arteriovenous malformations, and occlusive disease of the arteries of the neck and brain as causes for this condition.[3]

Although this paper does not primarily deal with cerebrovascular occlusive disease, the recent popularization of the use of anticoagulants in stroke problems makes it the duty of writers on this subject to stress the crucial importance of differentiation of

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From the Department of Neurosurgery, Temple University Medical Center.

Read before the Section on Nervous and Mental Diseases at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 9, 1959.

cerebral vascular occlusive disease from cerebral hemorrhage or even brain tumor; I shall discuss this problem later.

In 1951, I[4] reported before this Section on my experience with neurosurgical intervention in 30 cases of spontaneous intracranial hemorrhage, many of which simulated cerebral apoplexy; shortly thereafter 7 additional patients were included in the study.[4] This presentation is a follow-up report on the patients who survived the operation. Of the 30 patients 75% were between 40 and 66 years of age at the time of operation, the youngest 25, and the oldest 70 years of age; 15 were women and 15 were men. Blood dyscrasia was ruled out in all of these patients. Many of them were operated on before the routine use of arteriography had become established; this procedure was carried out in only four patients, and findings of aneurysm or vascular anomaly were negative in all instances. The preoperative clinical findings in all cases are listed in table 1.

TABLE 1.—*Summary of Preoperative Clinical Findings in Thirty Patients with Spontaneous Intracranial Hemorrhage*

	Patients		
Clinical Findings	No.	%	
History			
Hypertension	18	60	
Severe Headache	22	73	
Nuchal Rigidity (117 patients examined)	10	58	
Sensorium			
Awake	3	10	
Drowsy	13	43	90
Stupor or coma	14	47	
Dilated pupil on side of hemorrhage	7	23	
Choked disk	2	7	
Visual field defect	6	20	
Motor aphasia	4	13	
Mixed aphasia	3	10	
Hemiparesis	7	23	80
Hemiplegia	17	57	
Decerebrate rigidity	5	17	
Negative result of Wassermann test (25 patients examined)	25	100	
Spinal fluid (26 patients examined)			
Pressure elevated	24	92	
Red blood cells	20	77	
Roentgenographic evidence of pineal gland shift (22 patients, pineal gland calcified, 11)	11	100	

Indications for Operation

Although there are patients with spontaneous intracerebral hemorrhage who recover without operation and with varying degrees of disability, progressive hemmorhage results in death. It would be helpful to know what percentage of patients with proved intracerebral hemorrhage recover with medical treatment. However, without operation or autopsy, verification is impossible. Perhaps one could obtain such a series by cerebral angiography which might show displacement of vessels and thus provide indirect evidence of a clot; however, a tumor might show a similar picture. I do not know of any report of an adequate series in which, after cerebral angiography had suggested the presence of a hematoma, a patient recovered without undergoing an operation. The alternative is to review statistics of patients with intracerebral hemorrhage who were not operated on and to verify the hemorrhage by autopsy. Aring and Merritt[5] did this in 116 cases. They found that 8% of the patients had died within 24 hours, 21% within 1 to 4 days, 38% within 5 to 14 days, and 11% in 14 to 60 days. Rose[6] reported autopsy studies of 205 patients with intracranial hemorrhage, 80% of whom had died within 24 hours. Zimmerman[7] analyzed the records and autopsy material in 107 cases of spontaneous intracerebral hemorrhage. Ninety-four per cent of these patients had died after the first attack, and all of them were dead within five weeks of onset.

Cushing[8] in 1903 recognized the hopelessness of conservative treatment and stated, "In spite of the unfavorable results following operations in both my cases, the temporary amelioration of the severe symptoms is a sufficient justification for future attempts to afford surgical relief in certain carefully selected cases." Since Cushing's report, there have been many others, dealing with the removal of these hematomas, with varied mortality and morbidity.[9]

The indications for surgery in the patients reported in this paper were as follows: (1) symptoms and signs of increasing intracranial pressure such as drowsiness progressing to stupor or coma, stertorous respirations, decrease of the pulse rate to below 60 per minute and the respiratory rate below 16 per minute, increase in the spinal fluid pressure to above 160 mm. of water, and choked disks (if symptoms persisted for days); (2) neurological signs of focal brain involvement such as motor or sensory aphasia, visual field defect, hemiparesis, hemiplegia, or hemianesthesia, unilateral dilated pupil, unilateral convulsions, and decerebrate rigidity; (3) a roentgenogram of the skull showing a shift of the calcified pineal gland away from the suspected side of intracranial hemorrhage; and (4) an arteriogram showing a shift of arteries or veins which suggested a space-taking clot or showed an aneurysm or an arteriovenous malformation.

I avoided operating on patients with signs of extensive hemorrhage into the dominant internal capsule, because, if the patient survived, the added burden of motor aphasia in conjunction with the hemiplegia seemed intolerable. No patients with advanced cardiac, renal, or pulmonary disease were operated on. Decerebrate rigidity, although usually a sign for unfavorable prognosis, was no contraindication to operation, provided the patient's vital signs were favorable. A gratifying result (reported below) occurred in one patient with this complication.

The operation usually was an exploratory trephination which was enlarged to a small craniectomy. Occasionally a bone flap was elevated.

Mere aspiration of the liquid blood proved to be inadequate, and in the remaining patients it was necessary to remove the blood, aspirate or lift out the clot, and inspect and perform biopsy on the cavity wall. Frequently, only venous or capillary bleeding was found, which could be controlled by means of cauterization or the use of Gelfoam. I never could determine whether the venous bleeding was the cause of the clot or whether it resulted from the separation of brain tissue by the clot.

Biopsy of the hematoma and of the cavity wall was performed in 29 patients. An aneurysm was found in one and rupture of an artery without aneurysm in three; two patients were found to have a brain tumor, one a chorioepithelioma and the other a malignant melanoma; no obvious cause for the bleeding was found in the remaining 24 patients. If the cortex around the incision became concave at the end of the operation, the patient would usually survive; however, if the bleeding was controlled but the brain was markedly edematous, survival was unlikely.

Eleven of the 30 patients died in the hospital. Hence, the operative mortality for the entire series was 37%; or, if the two patients with hemorrhage into a brain tumor are excluded, 30%. Nineteen patients were discharged from the hospital after operation, and, in the 1952 report, the shortest follow-up period was three months and the longest seven years.

The anatomic location of the clot was an important factor in the death or survival of a patient and his subsequent neurological deficit. Twenty patients had hemorrhage into the internal capsule, seven into the temporal lobe area, and three into the subdural space.

Hemorrhage into Internal Capsule

Twenty patients suffered hemorrhage into the internal capsule, including the two with bleeding into a malignant tumor. Ten of these patients died in the hospital, the operative mortality thus being 50%, or 40% if the two tumor cases are excluded. Of the 10 patients who were discharged, 6 subsequently died, one after three months, 2 after five months, 2 after four years, and one after six years respectively.

Four patients are still alive at the time of writing (8, 9, 10, and 10 years, respectively, after operation). This constitutes a survival rate of 20% for eight years and longer for patients with hemorrhage into the internal capsule. The history of one of these patients is worth reviewing, because it illustrates a favorable outcome, over a long period, in what had appeared to be a hopeless situation.

Report of a Case.—A woman aged 25 years was admitted in January, 1949, with a history of right-sided headache for two days, followed suddenly by a left-sided hemiplegia and coma. She also had a history of hypertension. The patient was in a state of decerebrate rigidity, with stertorous respirations and a blood pressure of 230/120 mm. Hg. The spinal fluid was bloody, with a pressure of 260 mm. of water. Her condition was too critical for performance of skull roentgenography or angiography. Emergency performance of a small craniotomy revealed a large clot involving the right side of the internal capsule. After removal of the clot, the middle cerebral artery was seen spurting into the cavity; it was occluded with a silver clip. No aneurysm was found. This patient, under observation for 10 years, shows the maximal amount of recovery after severe internal capsule hemorrhage, her only handicaps being a useless hand, and unilateral partial drop foot. She has no headaches and leads an active life, doing her own light housework and working in her husband's drugstore. She had one convulsion nine years after operation and has had none since. On therapy with rauwolfia (Raudixin), her blood pressure fluctuates between 160 to 180 mm. Hg systolic and 90 to 100 mm. Hg diastolic.

Hemorrhage into Temporal Lobe and Its Adjacent Area

Seventy per cent of the seven patients with hemorrhage into the temporal lobe and its adjacent area were under 50 years of age; only 33% of the patients with hemorrhage into the internal capsule were below this age. Only two patients with hemorrhage into the temporal lobe area had hypertension, whereas 16 of the 20 patients with hemorrhage into the internal capsule had such a history. All of the patients with hemorrhage into the temporal lobe area survived the operation and were discharged from the hospital, but three of them subsequently died, and one could not be followed up.

Three patients who were operated on for hemorrhage into the temporal lobe area are still alive 7, 10, and 11 years respectively, after operation. This constitutes a survival rate of 50% for seven years and longer, as compared with a survival rate of 20% for eight years and longer for those patients who had been operated on for hemorrhage into the internal capsule. All three of the surviving patients have an occasional convulsion and are maintained on anticonvulsant therapy.

Hemorrhage into Subdural Space

Three patients had a spontaneous hemorrhage into the subdural space; one died 20 days after operation from an epidural hemorrhage, and the other two are alive 11 years after operation.

Neurological Deficits

All of the 10 patients who survived operation for hemorrhage into the internal capsule were left with serious neurological deficits. Five patients were completely hemiplegic and bedridden and subsequently died in nursing homes or hospitals, one three months, two five months, and two four years after operation. One hemiparetic patient was ambulant until six years after operation, when his condition deteriorated, and he finally died in a mental institution. One housewife is alert but hemiplegic eight years after operation but needs help in walking. One patient is alert but partially aphasic and hemiparetic nine years postoperatively and works in his wife's shop. Another is partially hemiplegic 10 years postoperatively and walks with a foot brace and cane. One housewife is alert and active 10 years after operation. She has drop foot and paralysis of the hand but walks with a foot brace and cane. Her case is given in detail elsewhere in this report.

All seven patients with hemorrhage into the temporal lobe area survived operation. Their neurological deficits are less disabling than those which occurred in the patients who had had hemorrhage into the internal capsule. The only deficit in three of these seven patients was a cut in the visual field, and all three continued with their preoperative occupations; one of them died 14 years after operation from heart disease, and another eight years after operation from hemorrhage into the opposite cerebrum. The third patient does housework 11 years after operation. Two of the patients with hemorrhage into the temporal lobe area have both a cut in the visual field and hemiparesis; both walk with foot brace and cane 10 and 7 years, respectively, after operation. One patient with astereognosis and hemiparesis died of a coronary attack seven months postoperatively. The remaining patient in this group of seven, who had mixed aphasia and hemiparesis, was discharged in an improved state but could not be located for follow-up investigation.

Postoperative Convulsions

Six (32%) of the 19 patients who survived operation have had one or more convulsion. Of the four patients who are still alive (two of them 8 and two 10 years respectively) after operation for hemorrhage in the internal capsule, one had a convulsion four months postoperatively and has had an occasional one since; another had a single convulsion nine years after operation and has had none since; the remaining two patients have had no attacks.

All three patients who are still alive 7, 10, and 11 years, respectively, after operation for hemorrhage into the temporal lobe area have had an occasional convulsion. The attacks began six years after operation in one case, after eight years in another, and after three years in the third. The attacks in all three patients have been controlled with anticonvulsants. The late onset of convulsions in some patients, six to nine years after operation, suggests that vascular changes about the healed lesion may be a factor. Howell[3d] reported an incidence of 35% of late "epilepsy" in 26 patients who survived operation for spontaneous intracerebral hemorrhage.

Autopsy Findings

Autopsies were performed on 10 of the 20 patients who had died either postoperatively or during the follow-up period. Hematomas into metastatic malignant brain tumors (chorioepithelioma and malignant melanoma) were found in two instances. Persistent hemorrhage, with softening and edema in an area of previous hemorrhage, was the most common cause of death. Atherosclerosis of the cerebral vessels was a frequent finding.

Focal hemorrhages into the pons in addition to the hemorrhage into the cerebral hemisphere occurred in three patients. These hemorrhages were probably caused by obstruction of venous drainage from the brain stem by the edematous cerebral hemispheres. However, Kaplan[10] believes that the hemorrhage into the pons is arterial and that this complication is found frequently in patients with spontaneous hemorrhage into the cerebral hemisphere. One patient who survived removal of a large hematoma from the left temporal lobe died nine years later from a massive hemorrhage into the opposite hemispheres and pons; no aneurysm was found.

Comparison of Long-term Follow-up Data with Other Follow-up Studies

I could find no reports of a series comparable to mine that had been analyzed with reference to location of the hemorrhage into the internal capsule versus other cerebral areas. Moreover, few of these studies dealt with long-term follow-up investigation. I had previously presented an analysis[4] of operative cases of spontaneous intracerebral hemorrhage which I had found in the literature through 1950. One hundred five cases had been reported by 20 different authors. Most of them had reported only a few cases; for example, 17 of the 19 reports had been on groups of less than 10 patients. The operative mortality varied from 0 to 100%.

The following surgeons reported 10 cases or more and some of their data might be comparable: Hamby[9a] described 14 cases with a mortality of 14%. However, none of his patients were designated as having hemorrhage into the internal capsule, and three had a hemorrhage into a metastatic tumor. Gurdjian and Webster[3b] published case reports of 11 patients with large hemorrhagic collections. Three of these patients had hypertension. One clot may have involved the internal capsule, and the rest were in the temporoparietal or temporo-occipital lobes. The operative mortality was 18%. Cerebral angiography was performed in 10 patients, and angiomas were found in 2; no berry aneurysms were reported. There were no follow-up reports on the survivors. Odom and co-workers[11] reported 106 cases of intracerebral hematoma. Fifty-five had been due to hypertension, 28 to congenital aneurysms, 9 to angiomatous malformations, and 14 had been of unknown etiology. Of 25 of their patients who had been operated on 5 died, an operative mortality of 20%. The authors gave no case reports or follow-up data. Their report dealt primarily with the pathology of these lesions. Ferey[12] reported 32 operative cases of intracerebral hemorrhage, 29 in the cerebrum and 3 in the cerebellum, with an operative mortality of 25%. However, he provided no case reports or follow-up studies. Beck[9b] reported 11 operative cases of spontaneous intracranial hemorrhage in patients between 35 and 62 years of age. Eight had had a history of hypertension. Six hematomas were located in the temporal, parietal, or occipital lobes; three in the frontal lobe; one in the middle of the fissure of Rolando; and the other in the inferior frontal lobe. Angiography was performed in 10 of 11 patients, but no vascular anomalies were reported. Six of the hematomas were subcortical and five were deep in the brain. All of Beck's patients survived operation and their progress was followed for from four months to three and one-half years. Beck stated that the results were excellent in one patient, good in eight, fairly good in one, and fair in one. No deaths occurred in the entire series. Since Beck did not give any case reports, it is difficult to determine how many of the lesions were in the internal capsule.

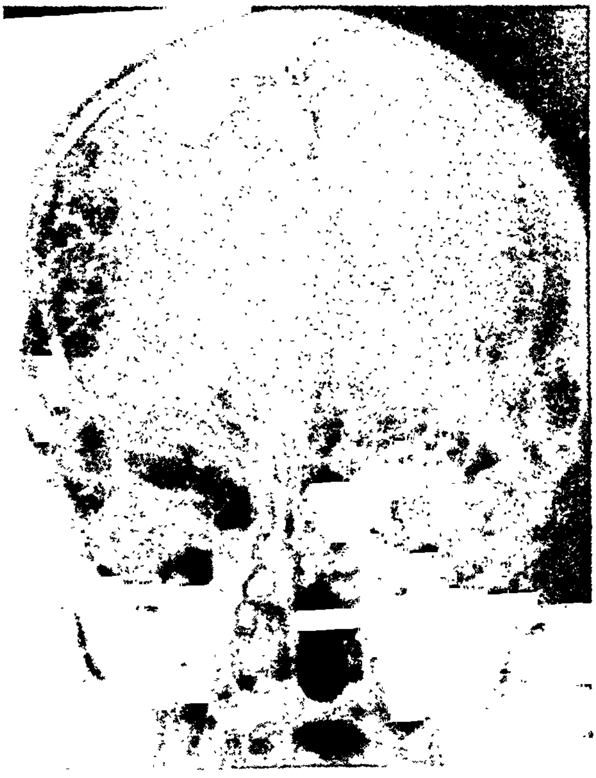

Fig. 1.—Angiogram showing arteriovenous malformation.

The report by Howell[3a] in 1957 of operative results in 33 patients with massive cerebral hemorrhage appears comparable to the group I am reporting. Howell reported a surgical mortality of 21% for his entire group, 43% for the group of patients with hypertension, and 5% in the nonhypertensive group. Cerebral angiography was performed in 24 of his patients. He found arterial hypertension to be the only demonstrable cause of hemorrhage in 13 patients; 5 patients (one of whom had hypertension) had a proved ruptured berry aneurysm; in 9 patients an arteriovenous malformation was shown by angiography; and in the remaining 6 patients no cause for the hemorrhage was found. He believed hypertension to be the most important factor influencing the outcome of treatment. Epilepsy developed as a delayed complication in 35% of the survivors in Howell's group.

Fig. 2.—Patient four weeks postoperatively after removal of malformation and intracerebral hematoma in right parietal lobe.

Summary of Additional Patients Operated on but not Included in Long-term Follow-up Investigation

Since my report in 1952,[4] eight additional patients have been operated on, one each by my associates, Drs. Wycis, Murtagh, and Lin, and the rest by Dr. Aldana and myself. Seven of this group of patients had hematomas involving the internal capsule and one had hemorrhage into the parietal lobe. Six patients had marked hypertension. One patient died the first day after operation from massive hemorrhage into the cerebrum and into the pons. Another died three weeks postoperatively from recurrent hemorrhage into the cerebrum. No autopsy was performed in either case. Six patients survived the operation and were discharged from the hospital. Thus, the operative mortality in this small group of eight patients was 25%.

TABLE 2.—*Differential Diagnosis of Common Causes of a "Stroke"*

	Hemorrhage		"Thrombosis"	Embolism	Brain Tumor
	Intracerebral	Subarachnoid			
Age group	Middle and old	Young and middle	Middle and old	Young and middle	All
Onset	Sudden	Sudden	Gradual	Sudden	Gradual
Progression	Usually rapid	Usually rapid	Usually gradual	Maximum deficit early	Usually gradual
Headache	Severe and usually on side of hemorrhage, early	Severe and generalized	Mild or absent; severe only if edema present	Mild or absent; severe only if edema present	Severe, early
Nuchal rigidity	Absent until bleeding ruptures into subarachnoid space	Marked and early	None	None	None, unless herniation of brain
Sensorium	Drowsy to coma	Drowsy to coma	Usually clear early, impaired if edema present	Usually clear early, impaired if edema present	Varies, clear early
Blood pressure	Hypertension (50%)	Usually normal early	Normal or moderately elevated	Normal or moderately elevated	Normal, but increases as intracranial pressure increases
Eye grounds					
Retina	May show hemorrhage	May show hemorrhage	No hemorrhage	No hemorrhage	May show hemorrhage if severely choked disk
Blood vessels	Hypertensive changes	Normal	Arteriosclerotic changes	Normal, or emboli visible	Veins dilated and tortuous
Disk	Normal, choked later	Normal or choked	Normal	Normal	Choked (40%)
Spinal fluid					
Pressure	Increased	Increased	Normal (130-160 mm. H_2O)	Normal	Increased
Color	Bloody in over 50%	Pink to frank blood, usually cherry red	Clear	Clear	Clear
Pineal gland on skull roentgenograms	Shifted to one side by clot	No shift	No shift unless edema present	No shift unless edema present	Shifted
Cerebral angiogram	Shift of vessels; visualization of aneurysm or arteriovenous malformation	Aneurysm or arteriovenous malformation	Occlusion of artery in cerebrum or internal carotid artery in neck	Occluded vessel may be visualized	Shift of vessels; tumor visualized by concentration of radiopaque medium

One woman, now aged 53 years, is still alive seven years after operation. She walks with a brace and cane; her blood pressure varies between 130 to 150 mm. Hg systolic and 80 to 90 mm. Hg diastolic. She had two jacksonian convulsions three years after operation but has had none since. She is on therapy with phenobarbital and reserpine (Serpasil). One male patient, now aged 59 years, is hemiparetic but walks with a leg brace four years after operation. He is alert and can read but he cannot practice his profession as a minister. His blood pressure was normal both before and after operation. Another male patient, now 22 years of age, had an arteriovenous malformation (fig. 1) and an intracerebral hematoma in the right parietal lobe. He has made a good recovery, retaining only a slight weakness of his foot (fig. 2) and he is working as a painter two and one-half years after operation; he also had two jacksonian convulsions.

The remaining three patients, all with marked hypertension and with hemorrhages into the internal capsule, have had their postoperative progress followed for one to two years. All are bedridden, with marked neurological deficits, and are in institutions for the chronically ill.

Cerebral angiography was performed in five of the eight patients; no berry aneurysm was seen in any one of the five, but an arteriovenous malformation was seen in one patient; a shift of the arteries and the deep cerebral veins, which suggested a space-taking clot, occurred in two patients; and no abnormality was found in the remaining two patients.

Importance of Differential Diagnosis of Cerebral Hemorrhage from Embolic or Occlusive Vascular Disease (Thrombosis) and Disease of Cerebral or Carotid Arteries in the Neck

In view of the recent tendency to popularize the use of anticoagulants in "stroke cases," it is important to emphasize the danger of the use of such substances in a case of cerebral hemorrhage which has been diagnosed as "cerebral thrombosis" or embolism. (The term cerebral thrombosis should be used only if confirmed by pathological examination.) Table 2 may be of help in the differential diagnosis of these conditions. However, cerebral softening may occur in the field of irrigation of an artery which has been occluded by "thrombosis" or embolism. Blood vessels in the softened area may weaken and rupture. Experimental studies with use of anticoagulants in animals with cerebrovascular occlusive disease show that these substances increase the bleeding into infarcts.[13] The danger in the use of anticoagulants in such a situation is obvious. The use of these drugs in the treatment of embolic, occlusive, or "insufficiency" states of the cerebral blood vessels should be abandoned until further experimental studies definitely prove the value of such therapy.

Summary

The operative mortality for removal of hematomas from the temporal lobe area is surprisingly low, and in the series here reported no postoperative deaths occurred. The residual neurological deficit is compatible with a useful and productive life. Fifty per cent of these patients are still alive 7 to 11 years after operation.

The operative mortality for removal of hematomas from the internal capsule is high, and both the preoperative and postoperative neurological deficit is marked. Probably all of these patients would have died without operation. Some of those who survived are active within the limitations imposed on them and are glad to be alive. Twenty per cent of this group are still alive 8 to 10 years after operation. This long-term survival rate compares favorably with that of patients operated on for malignancy of the lung, stomach, and other areas.

Prompt neurosurgical intervention for spontaneous intracerebral hemorrhage which causes focal neurological signs and progression in intracranial pressure will save lives.

3401 N. Broad St. (40).

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FREEDOM IN THE PRESENCE OF AN AUTHORITY FIGURE.—The analyst, although he stands as the advocate of individual integrity, inviolability, and spontaneity, is at the same time the initiator and agent of a process that for painfully long periods of time must be traced through a maze of submissiveness and intrusiveness. The necessity to assist the patient to the point of his "ego's freedom to choose" along a route of dependence, via the psychoanalytic processes of dynamic and genetic regression, constitutes a paradox, upon the solution of which depends the outcome of the therapy. There is no lessening of its stress from the fact that this paradox confronts every parent and indeed every authority-figure in a society where the privileges and obligations of the individual are traditionally honored.—S. L. Olinick, M.D., The Analytic Paradox, *Psychiatry*, November, 1959.

RECENT DEVELOPMENTS IN FORENSIC PATHOLOGY

Russell S. Fisher, M.D., Baltimore

Forensic pathology has become a subspecialty in the field of pathology within the past five years. The increasing contribution of pathology to the elucidation of the problems of trauma and the solution of the legal aspects of these problems emphasizes the great need for broadening the horizon of pathologists. The vast scope of this field is recognized when one considers that practically all homicide cases, nearly all compensation cases, and about 4 of every 10 tort cases or damage actions heard in the courts today involve medical testimony and require expert medical survey of the evidence on which the final decisions will be based.

The use of scientific developments in pathology in the solution of medicolegal problems, especially in the investigation of sudden and violent death, in the public interest has been far slower than any other application of pathology in the last 100 years. Indeed, except in a few cities and in the state of Massachusetts, it can be said that no progress occurred until 1939, when Maryland abolished its coroner system and established a centrally directed statewide medicolegal department. This included the adequate legal requirement that trained forensic pathologists assist local physician deputy medical examiners, whenever an autopsy was indicated, and a central toxicological facility. Virginia adopted this system in 1946, and a few other states have initiated improved coroner systems in the last decade. Even with this progress it was not until the last three years that forensic pathology gained recognition as a bona fide subspecialty in the field.

New Status of Forensic Pathology

The sequence of important events in the development of forensic pathology as a subspecialty of pathology is as follows.

1. The activities of the Committee on Medicolegal Problems of the American Medical Association under the leadership of such outstanding men as Regan, Holloway, and Moritz.
2. The establishment of the Committee on Forensic Pathology of the College of American Pathologists in 1954. This committee has been especially active in persuading the American Board of Pathology to establish the subspecialty certification in forensic pathology, which will be described subsequently in this paper.
3. The establishment by the American Society of Clinical Pathologists of its Council on Forensic Pathology, which is dedicated to the continuing education of pathologists and the improvement of the caliber of practice in this field.
4. The establishment in 1958 of the Registry of Forensic Pathology at the Armed Forces Institute of Pathology under the sponsorship of the College of American Pathologists. The function of this registry is to collect, classify, study, and register cases of a medicolegal nature. As a repository for such cases, the registry makes available material for research and teaching. It is anticipated that sufficient material can be assembled from contributing sources to provide a pool of pathological material to permit (*a*) research on unsolved problems of forensic pathology; (*b*) preparation of lantern slides, photographs, and microslides to be used in classes, seminars, and workshops; (*c*) use of gross material for seminars, schools, board examinations, museum specimens, and research; and (*d*) accumulation of data for publication.
5. The initiation of subspecialty certifications in forensic pathology by the American Board of Pathology. The first certificates were awarded at the meeting of the Board in Boston in April, 1959. The first examinations in this subject will be given in November, 1959, in New Orleans. The Board, in conjunction with the American Medical Association's Council on Medical Education and Hospitals, will inspect and approve centers for training in forensic pathology, thus establishing criteria of adequacy for practice and for training facilities for young men aspiring to work in this field.
6. During the past 12 years the National Municipal League has campaigned actively for better medicolegal statutes. Their booklet entitled "A Model Medicolegal Investigative Law" has been widely distributed and is of great value to local groups seeking to improve or replace their antiquated coroner systems.
7. The continuing carnage of automobile accidents and the realization, impressed on the public by the National Safety Committee and its Alcohol Test Committee, of the role of alcohol in many of these deaths has been instrumental in getting chemical test legislation passed in 28 states. Pa-

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From the Office of the Chief Medical Examiner of Maryland and Division of Forensic Pathology, Department of Pathology, University of Maryland Medical School.

Read before the Section on Pathology and Physiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

thologists have been in the forefront in many of the organized drives necessary to obtain such legislation, and they continue in supervision of the laboratory work integral to the implementation of these statutes.

These important items of progress may be said to have established forensic pathology on a firm basis as a subspecialty of pathology, dedicated to the application of scientific developments to the solution of problems in the public interest. The intensive and continuing support of the entire community of physicians in the United States is highly desirable in an effort to assure the courts and the public that medicine is indeed interested in the solution, on a scientific basis, of the many problems of medicolegal nature. The vast scope of this field is readily recognized when one considers that practically all homicide cases, nearly all compensation cases, and about 4 of every 10 tort cases or damage actions heard in the courts today involve medical testimony and require expert medical survey of important parts of the evidence on which the final decisions will be based.

Research in Forensic Pathology

With the maturation of forensic pathology as a respected member of the scientific disciplines there has been a tremendous emphasis in research on the pathology of trauma and its toxicological implications.

Perhaps the most widely studied of the new chemicals are the organic phosphates. These extremely toxic agents cause a marked depression of a vital enzyme system in poisoned persons. Demonstrations of such enzyme depression by application of chemical and histochemical techniques in blood and tissue specimens removed at autopsy are examples that may be of great use to forensic pathologists. The organic phosphates have been used as suicidal and homicidal agents.[1] More important has been the dissemination of information concerning the diagnosis of organic phosphate toxicity and the necessity of administering massive doses of atropine for its treatment.

Thallium poisoning has been recognized as an important medicolegal problem. The published experiences of Matthys and Thomas,[2] that fatal thallium poisoning is frequently confused with death due to encephalitis or the Guillain-Barré syndrome, has alerted pathologists without particular interest in the forensic field to the confusing picture caused by this chemical.

Many studies in the field of alcohol adaptation and tolerance have appeared in the last few years as well as important contributions describing the acidosis and hypoglycemia occasioned by the ingestion of compounds containing mixtures of ethyl and methyl alcohol, bay rum, isopropyl rubbing compound, and various other alcoholic substances, commonly described as "smoke."

Barbiturate addiction has been described as a clinical syndrome within the past few years, and the monumental work of Maurer and Vogel[3] has placed the diagnosis of this recently recognized addiction on firm clinical ground.

Such unusual poisonous agents as jellyfish and those unusual piscines known as "weevers," which are capable of producing extremely painful and even fatal wounds to swimmers and divers along the Eastern Atlantic and Mediterranean Coasts, recently have been described. Fatal poisoning as a result of eating the liver and flesh of the "blowfish" (tetraodon) gathered along the coast of Florida is the subject of a recent report of forensic interest.[4]

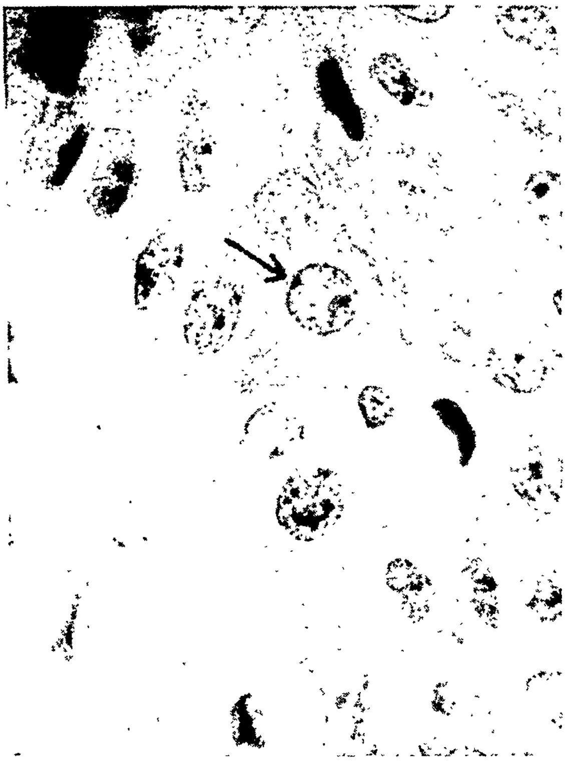

Fig. 1.—Female sex chromosome body in epithelial prickle cell (*arrow*) (× 900).

Finally, in the area of chemical poisoning there is renewed interest in carbon monoxide poisoning. A careful study by English colleagues, which demonstrates that some 30% of persons over 65 years of age cannot smell coal gas in concentrations of less than 50 parts per million (a potentially lethal level), has emphasized the ineffectiveness of odor alone as a danger signal for the accidental escape of unburnt gas.

Identification from immature bones and from the teeth as well as determination of sex by studies in cell morphology, particularly sexing by study of the chromatin particles in the nucleus of leukocytes and in fetal tissue (fig. 1), may be accepted as evidence of the increasing contributions to the literature of forensic pathology by the anatomist, the dentist, and the anthropologist.

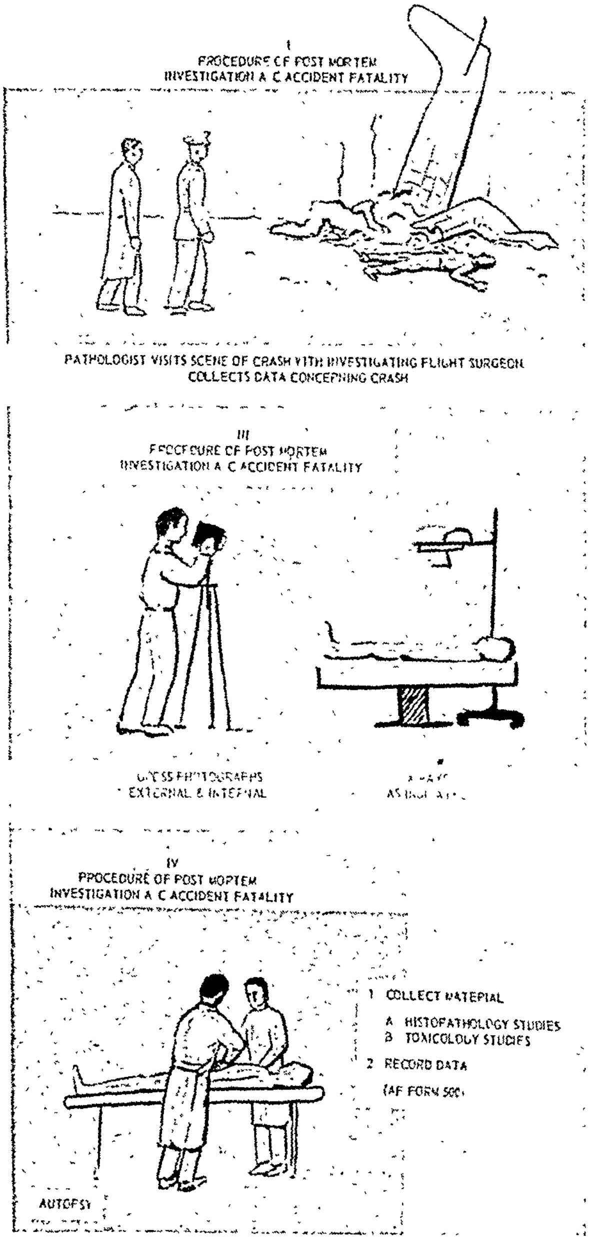

Fig. 2.—Selected procedures in investigation of aircraft accidents (illustrations provided by courtesy of aviation pathology section, Armed Forces Institute of Pathology).

A tremendous impetus in the study of the pathology of injury has been generated by use of the new supersonic airplanes in the U. S. Armed Forces and of the high-speed jet aircraft now appearing in commercial air-transport operations. One of the most interesting presentations in this area is that of Lawton[5] who demonstrated in pressure chamber studies that "pilots" were occasionally observed to collapse at pressures ordinarily considered to simulate safe altitudes. He observed that these patients were anxious and were hyperventilating. Fifty per cent of the trainees who encountered difficulties had usually had inadequate breakfasts, and in many cases hypoglycemia could be shown to be a factor in pilot failure. Such simple changes as alteration in the dietary regimen led to prevention of hyperventilation and hypoglycemia, with a consequent marked decrease in pilot-error accidents at one Air Force training base. The organization of a team of pathologists and toxicologists at the Armed Forces Institute of Pathology and of similar groups in civilian medicolegal practice stresses the importance of the pathologist as a member of the investigating group studying aircraft accident fatalities (fig. 2). The potential contributions of pathologists in the area are legion, yet the earliest documented recognition of the pathologist as an important member of the team has appeared within the last five years.

The increasing complexity of surgery made possible by surgical research and improved anesthesia has served to focus attention on the problems of anesthetic causation or contribution to operative death. The recognition of the dangers of excess carbon dioxide accumulation in patients with chronic chest disease and of the causation of atrial fibrillation by electric shocks in industrial situations are two examples of recent progress. The increasing perception that the cause of anesthetic fatalities is more often concealed in the method rather than in the type of anesthesia administered has been emphasized by Ruth and co-workers,[6] who have made an outstanding contribution to the field. These authors list hypoxia, hypercapnia, excessive anxiety, and errors in dosage as the most important factors in cardiac asystole. Other interesting studies in the field include those of Hale and Moraca,[7] who showed tracings obtained when the heart is under the direct control of the operator who causes cardiac asystole by injection of potassium citrate into the coronary tree. Surely, from studies such as these will arise a better understanding of the surgically and anesthetically produced cardiac arrests which are such a bane in the operating room today.

No review of recent developments in forensic pathology would be complete without some mention of "whiplash" injuries and the many attempts on the part of orthopedic surgeons, pathologists, and even attorneys to describe and delimit adequately the pathogenesis and the sequelae of injuries sustained by sudden disproportionate acceleration or deceleration of movements of the head and trunk.

Contributions of Forensic Pathology

The contributions in the medicolegal field of medicolegal pathologists to the recognition of anaphylactic reactions to penicillin deserve mention. Penicillin and other new therapeutic agents require continuing study in the determination of their dangers as well as their advantages.

The blood-grouping tests that have been developed in the past 15 years for use in disputed paternity proceedings are now recognized as compelling evidence in almost all states in the union. Just when we have begun to feel that the scientific method of disproving paternity was approaching the ultimate, the report of Sussman and Schatkin[8] emphasized the frailty of human nature. They reported 67 cases of disputed paternity proceedings in which the man did not contest the allegation of paternity. After the litigation was finished, A-B-O and M-N tests were run on a voluntary basis. In 12 of the 67 cases the serologic tests proved that the person who had submitted to the charge of paternity was not, in fact, the father of the infant in question.

Among the most disconcerting experiences in the life of a pathologist is that of reaching the conclusion of the gross, microscopic, and chemical studies in a case of sudden death and realizing that he has not been able to demonstrate, with the tools available, the cause of death. A small portion of such cases will now be solved by the development and refinement of the precipitin test for hypersensitivity. This test depends on the fact that in the test tube, particularly in agar-stabilized preparations, a positive result of a precipitin test may be demonstrated with use of a potent antigen and the serum or macerated tissue extract of the victim. Thus, in a recent case of hypersensitivity to horse serum in which the issue in dispute was whether the sudden death was due to sensitivity to penicillin or to the horse serum vehicle for tetanus antitoxin given simultaneously, our laboratory was able to demonstrate an excellent precipitin reaction in the tubes containing the patient's serum and the horse serum but no reaction in tubes containing the patient's serum and penicillin. Much further work is needed in refining this technique, but it has been demonstrated to be successful and leads one to hope that, in the near future, immunological studies will lead to the solution of a considerable number of medicolegal cases by demonstration of sensitivity reaction in cases of anaphylactic death.

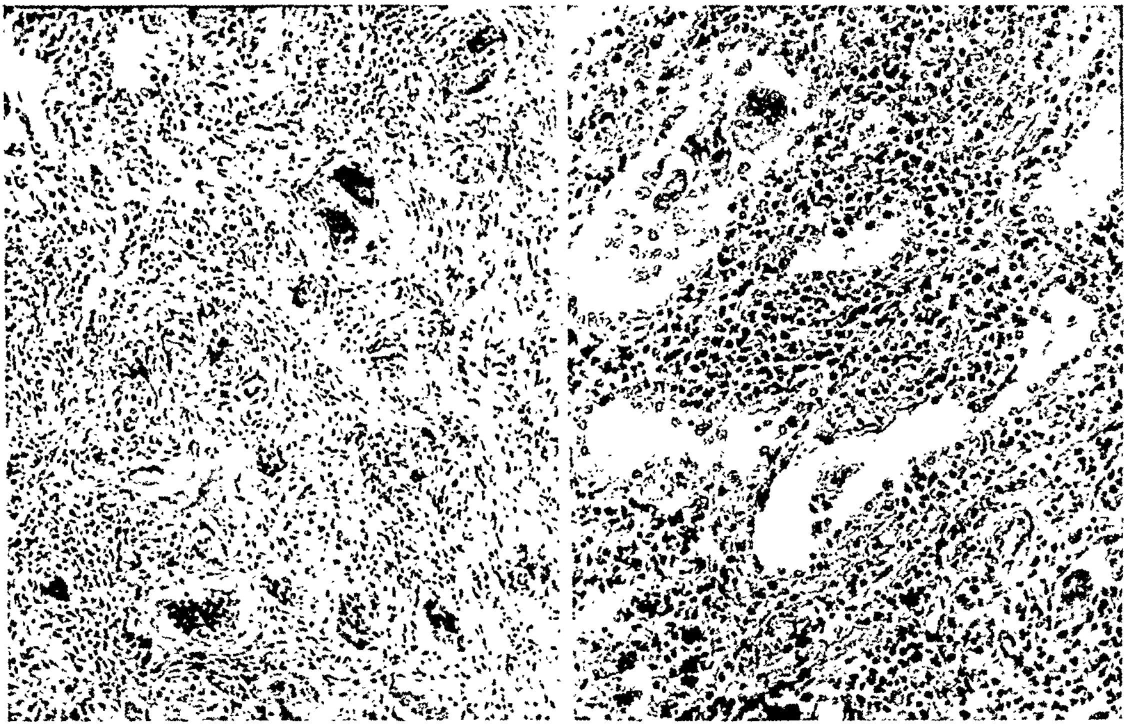

Fig. 3.—Pulmonary lesions in patients with, *left*, berylliosis (× 70) and, *right*, Hamman-Rich disease (× 100), selected to show similar granulomatous reaction.

The Gettler test for drowning was described nearly two decades ago. It depends on the assumption that, in persons drowning in sea water, the ingestion of highly saline water will lead to an increased blood chloride concentration in the left heart as compared to the right and, in persons drowning in fresh water, a dilution of blood chloride in the left heart as compared with the right. The test was widely used but was subject to considerable variation and, of course, was useless when drowning occurred in "brackish" water. The development and application to human cases by

Durlacher and co-workers[9] of plasma-specific gravity-dilution procedures has offered great assistance to the medicolegal pathologist in his studies of putatively drowned victims. The principle is simple, depending as it does on the fact that ingestion of water, whether fresh or salt, of low specific gravity leads regularly to the dilution of the plasma in the left heart. With the use of corrections for the contribution to the specific gravity by hemoglobin released through hemolysis of the cells, the procedure gives a great deal more certainty to the diagnosis of drowning than has been possible heretofore; typical findings are shown in the table.

Typical Atrial Plasma Differences in Victims of Drownings and Controls

	Specific Gravity*		
Cause of Death	L.	R.	L.-R.
Fresh-water drowning	1.0307	1.0349	—0.0042
Brackish-water drowning	1.0306	1.0323	—0.0017
Salt-water drowning	1.0319	1.0468	—0.0149
Cardiac failure	1.0291	1.0267	+0.0024
Hanging	1.0367	1.0381	—0.0014
Electrocution	1.0318	1.0287	+0.0031

* L. = left atrium; R. = right atrium. Specific gravity is corrected for hemolysis.

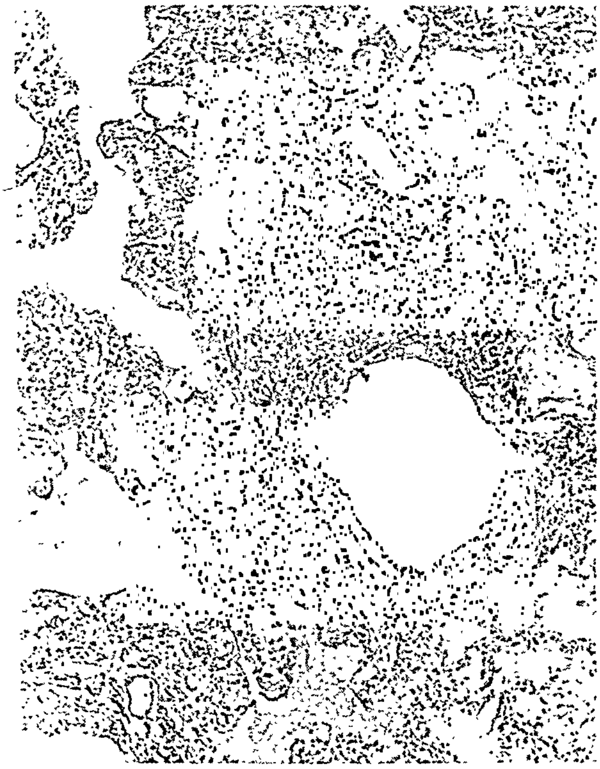

Fig. 4.—Lung of patient with acute "silo-filler's disease," showing endobronchiolitis and surrounding interstitial pneumonitis (× 70).

Pathological studies of the lungs in the last few years have produced three interesting conditions with which the medicolegal pathologist must be familiar. These are the diffuse interstitial fibrosis known originally as the Hamman-Rich syndrome which may readily be confused with beryllium pneumonitis. The second is the recently described granulomatous interstitial pneumonitis (fig. 3) resulting from the handling of a variety of dusty, moldy organic materials, described by Dickie and Rankin[10] under the title "farmer's lung." The third member of the pulmonary triumvirate of recent years is known as "silo-filler's disease"[11] (fig. 4 and 5). The occurrence of bronchiolitis obliterans due to inhalation of higher oxides of nitrogen, principally nitrogen dioxide, has been recognized as a laboratory accident in years past. Its recognition by Leib and co-workers[11] as the underlying pathological process leading to chronic pulmonary insufficiency in farmers who developed pneumonitis during silo filling is an excellent example of recognition of a chemical poisonous agent by its effect on the lung, with subsequent proof that the agent was, in fact, present in the environment where the disease occurred.

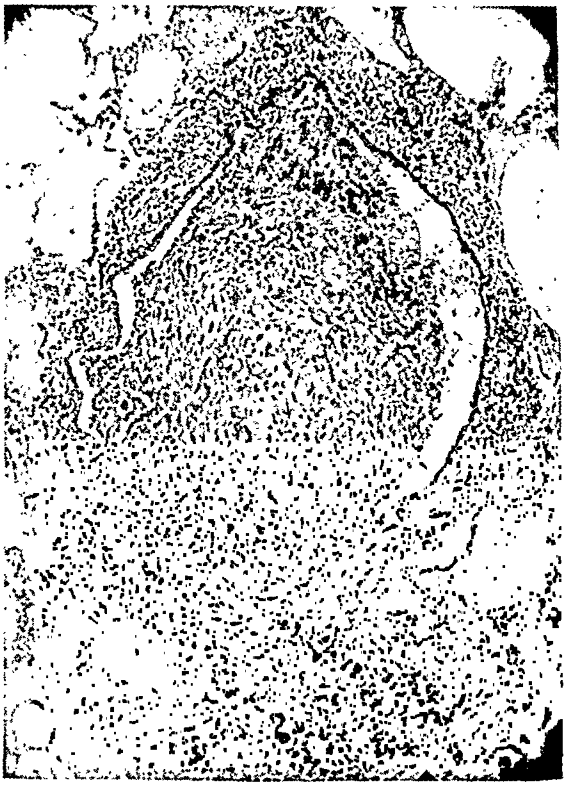

Fig. 5.—Obliterative endobronchiolitis; a later stage of "silo-filler's disease" or nitrogen dioxide poisoning.

Summary

Forensic pathology has emerged as a full-fledged subspecialty in the field of pathology within the past five years. The increasing importance of the contribution of pathology to the elucidation of the problems of trauma and the solution of the legal aspects of these problems emphasizes the great need for broadening the horizon of pathologists in the pathology of trauma.

Outstanding developments in the research laboratory in the past years include specific gravity procedure in downing tests, special techniques in investigating aircraft accidents, recognition of such new types of poisoning as "silo-fillers disease" and "farmer's lung," the development of a precipitin test to confirm hypersensitivity deaths, and studies in alcohol adaptation and tolerance.

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BILATERAL MIDLINE FIXATION OF CRICOARYTENOID JOINTS AS A SERIOUS MEDICAL EMERGENCY

Ira A. Polisar, M.D., Benjamin Burbank, M.D., Leon M. Levitt, M.D., Hyman M. Katz, M.D.
and
Thomas G. Morrione, M.D., Brooklyn, N. Y.

Inspiratory stridor, nonresponsive asthma, intermittent respiratory difficulty with cyanosis, sudden collapse, shock, and coma can all be observed in patients with midline fixation of the right and left cricoarytenoid joints. Each of these articulations has a ligamentous capsule lined by a synovial membrane and normally permits gliding and rotatory movements of the apposed articular surfaces. When they are ankylosed by local or general arthritis the consequences are serious. The case histories of a man 47 years of age and two women 51 and 56 years of age illustrate the severity of the symptoms, the bad effects of administering sedatives, the importance of considering tracheostomy, and the possibility of a fatal complication. The two female patients were permanently relieved by arytenoidectomy.

Hidden almost exclusively in the specialized otolaryngologic literature under the seemingly benign title "cricoarytenoid arthritis" appears a bizarre syndrome to which we would like to direct the attention of clinicians. A patient may present any one or a combination of the following signs: inspiratory stridor, nonresponsive asthma, intermittent respiratory difficulty with cyanosis, sudden collapse, shock, or coma. Prompt recognition and adequate treatment are lifesaving. This entity may result from bilateral midline fixation of the cricoarytenoid joints.

Background

Anatomy.[1]—Each of the cricoarytenoid joints has a ligamentous capsule lined by a synovial membrane. The capsule of the joint is strengthened posteriorly by a band which is inserted into the base of the arytenoid cartilage. The movements

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From the Division of Otolaryngology, Department of Surgery, and Department of Medicine, State University of New York, Downstate Medical Center; the departments of otolaryngology, medicine, and pathology, Long Island College Hospital; and the Brooklyn Veterans Administration Hospital.

which take place at the cricoarytenoid joint are gliding and rotatory. The structure of this joint places it in the category of diarthrodial articulations: it is composed of two cartilages which move freely on each other; there is a definite joint capsule between them; each has an articular surface; and each surface and the capsule are lined with a synovial membrane.

Fig. 1 (case 3).—Articular surface of arytenoid cartilage showing pannus-like thickening on surface of cartilage. Note disarrangement of cartilage cells. Superficial layers consist of dense fibrillar connective tissue. Hematoxylin-eosin stain (× 125).

Histopathology.—Histopathological material is exceedingly scarce since the cricoarytenoid joint is not accessible for biopsy. A biopsy specimen of the larynx proper does not yield any fruitful information, and such biopsy reports consist almost solely of statements to the effect that the larynx shows no malignancy or specific infection such as tuberculosis. Autopsy material is very limited, because the joint is not examined routinely. Histological sections of the excised arytenoid cartilages reveal destruction of the superficial cartilaginous cells. This change is accompanied by fraying and roughening of the surface. The cartilage shows irregular replacement by fibrous tissue. The pathological specimens show minimal fibrosis and lymphocytic infiltration of the small amounts of synovial tissue adherent to their edges. Figure 1 shows the right arytenoid cartilage from the patient in case 3 (see the table). Figures 2 and 3 show low-power and high-power magnifications of the arytenoid cartilage from the patient in case 5 (see table).

History.—Recent American and foreign literature contains few references to this condition. However, older otolaryngologic textbooks[2] and journals[3] described this condition under such titles as "Arthritis," "Ankylosis and Rheumatism of the Cricoarytenoid Joints," "Arthritis Deformans of the Larynx,"[3a] and "Perichondritis of the Larynx." More recently, several authors[4] have revived interest in this subject. In 1958, one of us (I. A. P.)[5] reviewed the entire subject in detail.

Clinical Manifestations

While Montgomery[6] has described an acute state of this condition in which there is dysphagia, hoarseness, tenderness over the larynx, and acute congestive edema of the arytenoid cartilages and the arytenopiglottic folds, none of our patients presented any of these findings. Actually, the striking feature of our patients was that their bizarre symptoms distracted attention from the larynx as the basic seat of the difficulty. Our own experience would seem to indicate that this disorder is an insidious, progressive, pathological process of a low-grade inflammatory or degenerative nature which does not produce early symptoms and signs of laryngeal involvement. So insidious and seemingly benign is this process that most of our patients had been diagnosed as psychoneurotics and were advised to have psychiatric evaluation.

We have been impressed by a history of stridor, "asthma," dyspnea, recurrent exacerbations and remissions, and, finally, by the dramatic and sudden collapse to which these patients may be subject.

Symptoms and Treatment of Eight Patients with Bilateral Midline Fixation of Cricoarytenoid Joints

Cases			Duration, Yr.	Symptoms*			Treatment	
				Asthma	Arthritis			
					On Physical Examination	History		
No.	Age, Yr.	Sex					Operation	Result
1	57	M	10	Yes	No	No	Arytenoidectomy	Excellent
2	58	M	8	No	No	No	Arytenoidectomy	Excellent
3	56	F	7	Yes	No	No	Arytenoidectomy, bilateral	Excellent
4	28	M	4	No	No	No	Arytenoidectomy	Excellent
5	51	F	5	Yes	Yes	Yes	Arytenoidectomy	Excellent
6	25	M	1	No	No	Yes	Arytenoidectomy	Excellent.
7	47	M	2	No	No	No	Tracheostomy	Died
8	70	M	1	No	Yes	Yes	Tracheostomy	Died

* All patients had stridor, minimal hoarseness, and dyspnea on exertion.

Stridor.—In every instance, questioning revealed that these patients are aware that they make loud noises which are most marked during inspiration. This crowing inspiratory stridor is easily confirmed by observation at the bedside. A carefully taken history reveals that the stridor is most marked when the patient is inactive, relaxed, or asleep and least marked when the patient is alert and active. We believe that patients are able to modify their extraordinary laryngeal obstruction when they are alert and that loss of this compensatory mechanism accounts for the stridor when they are relaxed or asleep. The validity of this thesis has been proved in several of our patients when they were given sedatives and when we observed how quickly the inspiratory stridor became accentuated. This reaction, in some instances, was promptly followed by severe cyanosis to such a degree that the need for emergency tracheostomy had to be considered.

"Asthma."—Most of our patients gave a history of being treated for asthma. In every instance in which this diagnosis was entertained, conventional methods of therapy were unsuccessful. In a review of the findings in these cases there was no familial or personal history of allergic manifestations; peripheral blood and respiratory secretions did not reveal eosinophilia; and most important, both patients and physicians were well aware that this disorder was an inspiratory rather than an expiratory difficulty.

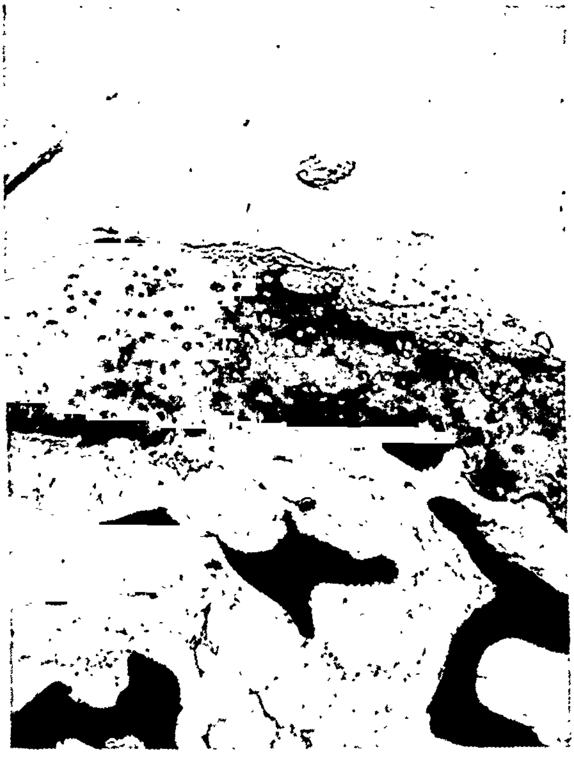

Fig. 2 (case 5).—Arytenoid cartilage showing destruction and roughening of cartilaginous articular surface. Hematoxylin-eosin stain (× 40).

Dyspnea.—Dyspnea has not been a serious complaint of most of these patients. With the passage of time, or in the presence of a superimposed upper respiratory infection, they have noted slight to moderate exertional dyspnea, but this symptom rarely has been disabling.

Exacerbations and Remissions.—Exacerbations usually were accompanied by an upper respiratory infection and were apt to continue for a long time after the manifestation of the concomitant infection had disappeared. There have been instances, however, in which exacerbations occurred without the stimulus of a superimposed respiratory infection or of any other etiological agent which we have been able to discover. In this latter respect, it seems to follow the course of rheumatoid arthritis involving the more commonly affected joints. Remissions have occurred in a similarly unexplained and unpredictable fashion.

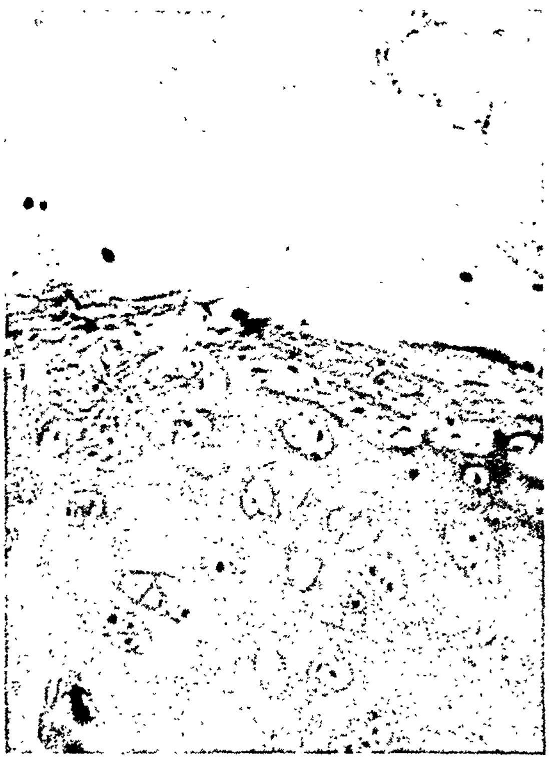

Fig. 3 (case 5).—Articular surface of arytenoid cartilage, showing destruction and disarrangement of cartilage. Roughened surface shows fibrous replacement of cartilage. Hematoxylin-eosin stain (× 125).

Collapse.—The patients presenting the most serious and dramatic cases were admitted to the hospital in a state of peripheral vascular collapse. It seems that the following sequence of events probably took place. An exacerbation occurred, usually as the result of an upper respiratory infection which augmented the existing hypoxia, with serious effects on the vital centers in the central nervous system. Clinically, this was manifested by marked restlessness. Sedation was given, and the medication inhibited the previous compensatory mechanism which had permitted the patient to suck air through the narrowed glottis. Thus a vicious cycle was established. Furthermore, the respiratory secretions, initially increased by the respiratory infection, were now retained, since hypoxia impairs both ciliary action and bronchial peristalsis. Further hypoxia may lead to coma and impairment of the cough reflex. In addition, local tissue anoxia may lead to transudation across the capillary membrane which could produce varying degrees of actual alveolar edema, augmenting further the hypoxic cycle. Finally, an infection may supervene, with the production of an extensive bronchopneumonia such as was found at autopsy in our patients who died (cases 7 and 8 in the table).

Hoarseness.—Since the vocal cords are in adduction, there is marked impairment of the airway but little impairment of vocalization. Hoarseness in these patients has always been mild, except in the presence of a superimposed, acute upper respiratory infection. It is our opinion that it is this absence of hoarseness which results in lack of attention to the actual seat of the trouble.

Diagnosis

Physical Examination.—The physical signs vary with the degree of fixation, the narrowness of the glottis, the presence or absence of acute, superimposed respiratory infection, and the therapy which has been given. In the absence of sedation or of infection, physical examination may be unrewarding. Audible inspiratory stridor is the chief sign. There is no accompanying hoarseness and little dyspnea or thoracic discomfort. While the stridor may or may not be accentuated by exertion, physical activity is impaired by exertional dyspnea. In some patients the striking finding is a history of long-term tracheostomy, with inability to remove the tracheal cannula without causing a recurrence of the stridor and even a sense of suffocation.

In the presence of superimposed upper respiratory infection, restlessness and mental confusion are the earliest signs. The stridor becomes more prolonged. Dyspnea, cyanosis, and tachycardia follow. Eventually coma and peripheral vascular collapse may occur.

The clinical picture may be confused further by the signs of bronchopneumonia. The latter tend to overshadow the importance of the basic pathological process and the therapeutic regimen may incorrectly stress the control of the infection at the cost of overlooking relief of the obstructed airway. The true diagnosis can be established by direct laryngoscopy with the "passive mobility" test described by Jackson.[7] The rigid fixation of the ankylosed arytenoid joint is strikingly different from its free, passive mobility in cases of paralysis of a vocal cord.[8]

Evidence of generalized rheumatoid arthritis may be present, although in our series, most patients (6 of 8) did not present any such findings.

Differential Diagnosis.—Once the diagnosis of a narrowed glottis has been entertained, the differential diagnosis rests between midline fixation of the cricoarytenoid joints and the presence of a bilateral paralysis of the recurrent laryngeal nerve. Major operation on the anterior neck and/or mediastinum has been known to produce such bilateral nerve paralysis. In the absence of such surgery, it has been postulated that either a central neurological lesion or a massive pathological process in the anterior mediastinum and neck may paralyze both nerves. It appears unlikely that any neurological lesion could involve both vagi exclusively and yet spare the nuclei of the glossopharyngeal, spinal accessory, and hypoglossal nerves which are in such close proximity to the vagal nuclei. Equally, it is just as difficult to visualize an intrathoracic lesion large enough to involve both recurrent laryngeal nerves without producing very obvious symptoms and signs. Therefore, in the absence of any surgical scars in the neck and anterior wall of the chest, this clinical picture is likely to be produced solely by bilateral fixation of the cricoarytenoid joint.

Treatment

Because the basic difficulty consists of an obstructed airway, the only definitive therapy is surgical.[9] In all cases, this therapy will consist of a combination of arytenoidectomy or arytenoidopexy preceded by elective or emergency tracheostomy.

Some patients are first seen because of acute respiratory distress. For these, emergency tracheostomy is essential to avoid the vicious cycle which follows the establishment of progressive hypoxia, retention of sputum, or both. For patients with bacterial infection, administration of appropriate antibiotics is of value.

Hypoxia and retention of sputum are conditions which must be alleviated as quickly and efficiently as possible. The restlessness seen in these patients is always due to hypoxia and should never be treated by the administration of sedatives which inevitably increases the patient's difficulties. Since there is no retention of carbon dioxide, therapy with oxygen can be given with safety. Retention of sputum is best treated by frequent aspiration of the retained secretions. Viscosity of these secretions can be diminished greatly by the intratracheal instillation of detergents, proteolytic enzymes, or both, followed by aspiration through the tracheostomy. After the immediate emergency has been controlled and all evidences of infection have been eliminated, definitive surgery may be performed.

It is tempting to use steroids in an effort to alleviate the acute exacerbations, because these drugs are of value in the symptomatic control of peripheral rheumatoid arthritis. In the two cases reported by Montgomery,[4a] both patients received steroids because of disseminated arthritis; yet one died of an acute exacerbation of cricoarytenoid arthritis, and the other died from acute cholecystitis with cholelithiasis and pneumonia. In our experience, steroids have been given to patients who had stridor as their sole complaint, but no improvement was seen. In other cases, similar to those of Montgomery, we have seen acute exacerbations while the patients were receiving adequate doses of steroids. In view of these observations, it is our impression at present that steroids are not of value in the control of this lesion. Indeed, because of their role in increasing susceptibility to infection, they are probably contraindicated.

Reports of Cases

Case 3.—A 56-year-old woman was admitted to the hospital with a seven-year history of attacks of dyspnea associated with a crowing noise. The attacks lasted from several minutes to many hours. During this time she noted gradually increasing exertional dyspnea, but she was still able to perform her usual chores as a housewife without difficulty. Several times she had been given tests and treated for asthma, but no relief was obtained. She had been told also that her difficulties were due to nervousness, but she had not had any psychiatric therapy.

The crowing noise, which represented her chief difficulty, occurred almost every night while she was sleeping, when she was fatigued, or after unusual exertion. The noise was said to be so loud that it could be heard in another room. On physical examination she was found to have slight respiratory distress and to make loud, crowing inspiratory noises. The remaining findings of the general physical examination were normal, and results of all laboratory studies were negative.

During the first night in the hospital she was given a barbiturate at bedtime and about one hour later was found to be semicomatose. Respiratory distress was marked, cyanosis was evident, and a loud inspiratory stridor could be heard at both ends of the long hospital corridor. In about four hours this dramatic episode subsided spontaneously. The next day, direct laryngoscopic examination revealed that both vocal cords were fixed in the midline, with a glottic chink less than 2 mm. wide. The arytenoid cartilages and the vocal cords could not be abducted passively. Again, the patient was given a barbiturate, and soon the same dramatic chain of events occurred. Subsequently, a tracheostomy was performed to establish an adequate airway.

During the next three months she was treated with steroids, but there was no change in the arytenoid fixation. The steroid therapy was discontinued, and an arytenoidectomy was performed on the left, resulting in moderate improvement in her exertional dyspnea and stridor. Two years later, an arytenoidectomy was performed on the right, and, since then, she has had complete freedom from "asthma" and dyspnea.

Case 5.—A 51-year-old housewife was admitted with a history of recurrent wheezing and "collapse." She had active rheumatoid arthritis. Five years before, she had been hospitalized because of "collapse" from which she recovered spontaneously. No diagnosis was made at that time. Three years later she developed wheezing, which was diagnosed as asthma, but both the study of and therapy for this disorder were disappointing. Six months before admission she developed marked hoarseness and became acutely dyspneic. She was hospitalized elsewhere because of rapidly developing respiratory distress, cyanosis, collapse, and unconsciousness. The collapse and coma were relieved shortly after a tracheostomy had been performed. At this time she was told that her shock was due to acute adrenal insufficiency. Later, the tracheostomy opening was closed, but this action was followed by wheezing, dyspnea, and unusual fatigue on exertion. These symptoms progressed so rapidly that she required another tracheostomy. At this time she was told that emotional factors were playing a great part in her difficulties. She was advised to have psychiatric consultation but did not accept this advice.

On physical examination, it was noted that she was wearing a tracheotomy tube. There were evidences of active rheumatoid arthritis involving the small joints of both hands, wrists, elbows, and knees. She had subcutaneous nodules over both elbows. Except for a rapid erythrocyte sedimentation rate of 57 mm. per hour (Wintrobe) a positive C-reactive protein value, and a high latex-fixation titer, results of all her laboratory studies were normal. Direct laryngoscopy revealed that the vocal cords were fixed in the midline with a glottic chink of 2 mm. The anterior two-thirds of the cords could be bowed, but both arytenoid cartilages were fixed so that abduction was not possible. At this time she refused surgical intervention, and she was given a trial of steroid therapy. This medication relieved the symptoms of the peripheral arthritis but did not affect the cricoarytenoid fixation. Subsequently an arytenoidectomy was performed on the right, resulting in relief of her symptoms. Microscopic examination of the arytenoid joint surface revealed arthritis.

Case 7.—A 47-year-old truck driver was admitted because of generalized weakness of one year's duration. Two years prior to admission he had been studied in another hospital because of weakness and dyspnea. No diagnosis was made, and his difficulties subsided spontaneously for one year thereafter. Then he noted increasing exertional dyspnea, associated with loud crowing noises. This disturbance interferred with his speech so that even his wife had difficulty in understanding him. Three months prior to admission he had an acute, severe episode of dyspnea. He was told that his distress was due to nervousness, and he had accepted this verdict so thoroughly that he now shrugged off all his symptoms as evidence that he was a nervous person. Although he had been able to continue driving a truck, his wife reported that he had been exhausted after work, dozed constantly during off-duty hours, and sometimes slept for an entire weekend except when awakened for meals. For about one month he had suffered several frightening moments when transient "spasms" of the throat made it difficult for him to maintain control of his truck.

On admission, the only positive findings consisted of minimal hoarseness and slight tachypnea. Results of all laboratory tests were normal. At 1 a. m. the patient complained of a sudden pain in the throat, and this symptom was followed by an episode of severe dyspnea which subsided in a few moments. Because of his agitation, he was given 25 mg. of promazine (Sparine) hydrochloride intramuscularly. At 8 a. m. he was found to be cold, clammy, pulseless, tachypneic, and completely unresponsive and areflexic. Shortly thereafter his breathing was stertorous, with short periods of apnea and cyanosis. The blood pressure was 60/40 mm. Hg. The administration of metaraminol (Aramine) bitartrate and oxygen restored his blood pressure to 140/90 mm. Hg. The result of a spinal tap was normal. Direct laryngoscopy revealed a mild, diffuse inflammation of the larynx. The cords were fixed in adduction. An emergency tracheostomy was done at noon, and by 11 p. m. the patient had made a full recovery, even to the point where he was able to occlude the tracheostomy tube with his finger so that he could talk. He was lucid and spoke coherently. An x-ray film of the chest at this time showed bilateral congestion and edema and probable pneumonia on the left side.

The next morning the patient became cyanotic, and the intermittent apnea recurred. His blood pressure fell precipitously, and he became unresponsive. The tracheostomy tube was functioning well, and thorough aspiration was done through it. Levarterenol bitartrate, intravenously administered hydrocortisone sodium succinate (Solu-Cortef), and large doses of crystalline penicillin were given. A mechanical respirator with chest cuirass was used to assist respiration. Nevertheless, his condition gradually deteriorated, and he died the following morning. Autopsy revealed widespread suppurative bronchitis and pneumonia and fixation of the cricoarytenoid joints in the midline.

Summary and Conclusions

It is known that the cricoarytenoid joints may become ankylosed as the result of arthritis, with resultant fixation of both vocal cords in the midline. Since this apparently benign condition (many such patients being diagnosed as psychoneurotics) presents itself in the form of a bizarre syndrome and may result in death, a careful differential diagnosis is essential. The points to be watched for are recurrent exacerbation and remission of stridor, nonresponsive asthma, and dyspnea. Finally, dramatic and sudden collapse may occur. Both careful diagnosis and treatment consisting of preliminary tracheostomy, followed by one of the various procedures for arytenoidectomy or arytenoidopexy, may prove lifesaving.

142 Joralemon St. (1) (Dr. Polisar).

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IDIOPATHIC PAROXYSMAL MYOGLOBINURIA

Capt. Paul J. Phillippi, Capt. Frederick R. Jones
and
Lieut. Col. Wilbur L. Kenoyer, (MC), U. S. A. F.

Acute attacks of muscle pain occasionally so severe as to cause pseudoparalysis, associated with the appearance of myoglobin in the urine, and due to an unrecognizable cause have been given various names of which the most frequently used is idiopathic paroxysmal myoglobinuria. We have been able to find only 37 cases reported in the medical literature.

Myoglobinuria may occur from death of striated muscle due to crushing injuries, high-voltage shock, or arterial occlusion (anterior-tibial syndrome). The reason for the myoglobinuria is easy enough to understand in such cases, but why healthy people should experience sudden attacks of muscle pain associated with the appearance of myoglobin in the urine has been a mystery since the first case was described in 1911.[1]

The following case report is presented to re-emphasize some interesting facets of the problem.

Report of a Case

A 22-year-old white male basic trainee, who had been an outstanding athlete at the University of Georgia, experienced an episode of painful, tight thigh muscles on May 6, 1959, while on bivouac training. When he attempted to "walk the stiffness out," the pain increased in severity, and he complained of inability to move his legs. Tightness and pain in the arms, shoulders, and the calves of his legs were present to a lesser degree. A few hours after the onset of the pain physicians observed no objective changes and the patient was allowed to rest overnight. The next day he noted that his urine had turned dark brown, and the thigh pain and tenderness continued. Since the pain and dark color of the urine persisted, the patient was admitted to the hospital for evaluation and treatment on May 8.

The patient was a well-developed, muscular, athletic-appearing man who appeared in mild distress from painful thighs. The vital signs on admission were all normal and remained normal throughout the hospital stay. All the muscles of both thighs were moderately spastic. The patient complained of pain on motion or palpation of the thigh muscles, especially the left quadriceps. Except for absence of the patellar reflexes, neurological examination revealed no other evidence of sensory loss or reflex change.

Admission laboratory information showed a white blood cell count of 8,527 per cubic millimeter, with a normal differential count. The hematocrit value was 47%, and the platelet count was 200,000 per cubic millimeter. The erythrocyte sedimentation rate (Wintrobe) was 36 mm. per hour, and the serum potassium level was 4.8 mEq. per liter. The plasma hemoglobin level was less than 100 mg.%, and the blood urea nitrogen level was 30 mg.%. The dark brown urine had a specific gravity of 1.020 and contained protein (1+), a few granular casts, and an occasional red blood cell, with three to five white blood cells per high-power field. There was a strongly positive benzidine reaction, and results of examinations for porphyrins with use of Watson's reagent were negative. [illegible] of the thighs and abdomen show[illegible] On the third hospital day the level of serum transaminase was 143 units and that of serum creatinine 1.36 mg.%. The total serum bilirubin level was 0.5 mg.%. Biopsy specimens of muscle taken from the left quadriceps on the second hospital day and from the right quadriceps on the fifth hospital day both revealed normal muscle.

Clinically the patient gradually improved, and his urine was grossly clear on the fifth day of illness. His urinary output remained normal, and on the 13th day of illness the urinary sediment had cleared. At this time the patient was able to undergo mild, passive exercise of the lower extremities without pain or other evidence of recurrence. Four days later the patient complained of mild thigh pain and all exercise was discontinued for two days, during which time the urine remained normal. During the remainder of the convalescent period he underwent passive exercise, and by the 30th day he was able to perform mild, active exercise without difficulty. Findings of repeat laboratory studies at this time were all normal.

Comment

The etiology of this rare disease is obviously unknown, as the name implies. It has been suggested by some[2] that a familial predisposition may exist. A relationship to progressive muscular dystrophy[3] has been mentioned, but most of these patients have no apparent familial history. Electrophoretic studies have failed to demonstrate any difference between the myoglobin of these patients and that of normal persons.[4]

Clinically the disease is characterized by a sudden onset of pain and tenderness of the muscles, most frequently in the lower extremities. The degree

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From the Department of Medicine, U. S. A. F. Hospital, Lackland Air Force Base, Texas.

of involvement seems to vary greatly from a mild discomfort relieved by rest to a severe process which may cause "pseudoparalysis" and involve all skeletal muscles in the process.[5] The myoglobin appears in the urine within a few hours and may discolor the urine from light brown to dark red. The muscle pain and tenderness usually clear up with rest in a few days. It is rare for the muscle degeneration to be severe enough to lead to death,[5] but acute renal failure has been observed several times [6] and presents a serious threat to the patient's life.

Apparent precipitation of this disease by exercise has been reported in almost one-half of the cases, but Bowden pointed out that this has not been a factor in women. The first attack usually occurs in childhood or adolescence, although it may not occur until middle age,[5] and cases have been reported of attacks occurring as early as at 2 years of age.[7] Males are involved more frequently than females, and only one case has been reported in a Negro.[4] In most patients who have been followed up for a sufficient length of time, recurrences were observed.

The finding of benzidine-positive or guaiac-positive urine without red blood cells should lead one to suspect this diagnosis, and in association with these findings albuminuria and casts may be found. When red blood cells are found in the urine, lower nephron nephrosis should be suspected and an elevated blood urea nitrogen level with other evidence of acute renal failure should be looked for. If the plasma hemoglobin level is high enough to produce hemoglobinuria, the plasma will be discolored, as can be readily determined. Elevations in the levels of serum transaminase and creatinine have been recorded, but serum bilirubin levels have been normal.

Myoglobin differs from hemoglobin in that it has a much smaller globin fraction. Although both contain the same percentage of iron, myoglobin contains only one atom of iron compared to the four atoms in hemoglobin. The molecular weight of myoglobin is about 17,500 as compared to 68,000 for hemoglobin.[2] This accounts for the difference in the renal threshold of the two pigments (about 20 mg.% for myoglobin and 100 mg.% for hemoglobin). In most of the cases studied the definitive identification of myoglobin has been achieved by spectrophotometric means. This is a technically difficult procedure as well as one that is seldom available. Recently a method of identification by means of paper electrophoresis and a peroxide-benzidine stain [4] was described. Blondheim and co-workers [8] recently described a chemical test for screening urine for myoglobin.

In the case reported here the two muscle biopsy specimens were within normal limits; in most other cases in which muscle biopsy has been done, however, changes from swelling and patchy regression of muscle fibers to fragmentation and liquefaction have been described.[6b] These findings are limited to skeletal muscle. In cases in which acute renal failure occurred studies revealed acute tubular necrosis.

Treatment at the present stage of our knowledge is limited. Strenuous exercise should be avoided where it seems to be a precipitating factor, and rest during the acute phase of the attack is indicated. One should be aware of the possibility of acute renal failure and start treatment promptly.

Summary

A patient demonstrated several classic findings of idiopathic paroxysmal myoglobinuria. These findings included (1) acute onset of thigh pain and tenderness while exercising, (2) a feeling by the patient that he could not move his legs (pseudoparalysis), (3) the onset of dark coloration of the urine a few hours after the muscle pain, and (4) a strongly positive benzidine reaction on red cell-free urine at a time when the plasma was clear and contained less than 100 mg.% of hemoglobin.

A review of the literature on this rare disease emphasized the importance of renal complications, the probability of recurrent attacks, and the need for caution by the patient with regard to future exercise.

118 Nightingale Dr., San Antonio 11, Texas (Capt. Phillippi).

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USE OF IPRONIAZID IN TREATMENT OF ALCOHOLICS

Julius C. Travis, M.D., San Francisco

Twenty patients with histories of alcoholism were given iproniazid during recovery from bouts of heavy drinking. Iproniazid was administered to prevent or mitigate severe mental depression that often occurs in these patients. It was considered that the hazard of the hepatotoxic effect of iproniazid was less than the hazard of suicidal attempts in patients so severely depressed. None of the patients was known to have damaged livers before treatment. Polyvalent vitamins were administered concomitantly with iproniazid to prevent peripheral neuritis and liver damage. Sixteen patients had fair to excellent reversal of depression, anorexia, and insomnia; nine required less than 100 mg. of iproniazid daily. None of the patients developed liver complications or required hospitalization. There were no attempts at suicide.

For several years medical articles have reported the value of treatment with *iproniazid* (*Marsilid*) phosphate in patients with severe depression, agitated depression, and even schizophrenic depressed catatonia, but so far no report has appeared on the use of this drug in alcoholics. Because of its specific hepatotoxic effect[1] the drug was, and apparently still is, considered dangerous for the alcoholic patient, who already may be a victim of liver disease. For this reason I at first opposed its introduction into the adult guidance center of the San Francisco Department of Public Health, where alcoholic outpatients constitute the majority of the case load. However, the availability of such an unusual medicament for treatment of depression[2] eventually posed the question of its utility in selected patients with alcoholism who had no history or current evidence of liver disease.

Severe Depression in Alcoholics

After a protracted bout of heavy drinking there follows a period of sadness, remorse, and guilt which is difficult for the alcoholic patient to tolerate. He is almost driven back to drinking but usually lives through to happier days. During this period some patients may become deeply morose, have severe anorexia and troubled sleep, and feel left out of life, unable to communicate with friends or members of their own families. They begin to consider death as the only release from a mood which inexorably grips them tighter and tighter. Sedatives do not always help, vitamins fail to stimulate appetite, and mood-elevating drugs of the ephedrine type only seem to increase their anxiety.[3] Nor will other drugs reduce the anorexia, which is often so severe that any question of eating is answered by a facial grimace indicating such repugnance, if not actual nausea, that the feeling is communicated all too well to the examiner.

If, after days and weeks of treatment the medicaments given by the physician prove fruitless, the patient most frequently resumes drinking. If he does not, he may have to be referred to a psychiatric hospital for inpatient treatment. Finally, he may commit suicide.

Another type of depression, seen after a relatively minor drinking bout, occurs in persons with average moral values and acceptable behavior who have slipped back into old habits. The patient feels deeply ashamed, worries about the visible evidence of his lack of mature control and will power, may doubt his sanity, and may entertain ideas of self-destruction. In my experience most patients of this type usually recover as easily as the first group. Ordinarily one only needs to use safe and standard medicaments, encouragement, and realistic optimism to help these patients.

A third type of patient is the one who begins to drink as an escape from depression over family troubles, loss of job, and other worries. The drinking period may be relatively short, for alcohol has a limited value in combating depression, especially if it is severe. By the time the patient sees a physician, he has sunk into a mood of despair, all his old contrivances for dealing with the problems of life have failed, and he cannot place the blame on alcohol, for it is perfectly clear that he was in bad condition before he started drinking. He may also feel guilty of being an alcoholic because of his recent behavior. Hopeless to the extreme, he speaks openly of committing suicide. If he refuses to become an inpatient, and if there is not enough time to obtain a legal commitment, he may be willing to try a few days of medical treatment.

Most of these alcoholics, even outpatients, should be seen daily and given encouragement and consolation. This also provides frequent periods of observation, so that drug therapy can be adjusted in time or other appropriate action taken.

From the Adult Guidance Center, San Francisco Department of Public Health.

Treatment of Twenty Alcoholics with Iproniazid

The danger of suicide forces the physician to consider these cases deeply; I have often wished to do more for my patients than I felt was safely possible. Finally I decided to try therapy with iproniazid in one patient with a seemingly very dangerous depression. I felt that this patient, a woman aged 45 years, would shortly destroy herself if nothing were done. Compared with this, the remote risk of liver complications seemed minimal. Even if they did develop, she might have a better chance of living with iproniazid treatment. She denied any history of liver disease and did not have a swollen or tender liver.

This woman's treatment was begun with administration of 150 mg. of iproniazid per day. The results were startlingly successful; within 24 hours she began to eat and felt better than she had in several years. This impelled me to try iproniazid therapy in a small series of five similar patients. Though none experienced the sudden recovery of the first, all but one showed good or excellent results from treatment.

TABLE 1.—*Iproniazid Therapy in Twenty Mentally Depressed Alcoholics, Without Liver Damage*

Case, No	Sex	Age, Yr.	Iproniazid, Initial Daily Dose, Mg.	General Psychiatric Diagnosis	Effect of Therapy	Notes and Remarks	Total Duration of Treatment, Wk.
1	F	45	150	Agitated depression	Excellent	Increased appetite within 24 hr.	2
2	M	39	150	Inadequate personality	Good	Insomnia persisted	6
3	F	39	150	Passive-aggressive personality	Good	Aided by psychotherapy	13
4	F	45	150	Compulsive personality	Excellent	Panic relieved in 4 days	9
5	M	49	150	Passive-aggressive personality	Fair	Lassitude persisted	8
6	F	40	150	Passive-aggressive personality	Excellent	Quick response	6
7	F	40	50	Schizophrenia, paranoid	Excellent	Quick response; psychotic became activated in 2 wk.	8
8	M	43	50	Psychoneurosis, anxiety type	Good	Still insomniac	2
9	M	39	100	Passive-aggressive personality	Excellent	Has continued use of drug	40
10	F	36	50	Psychophysiological reaction	Poor	Changed to therapy with promazine hydrochloride	2
11	M	35	50	Psychoneurosis, character disorder	Poor	Drank, drug therapy discontinued	1
12	M	42	50	Anxiety type depression	Good	Able to accept psychotherapy	18
13	M	60	50	Compulsive personality	Fair	Slow response; late in treatment improved further	7
14	M	46	50	Inadequate personality	Poor	Resumed drinking	4
15	M	39	50	Character disorder	Good	Slow change	8
16	F	67	25	Adult situational reaction	Excellent	Changed in 2 days	12
17	F	38	50	Passive-aggressive personality	Good	Enabled to begin psychotherapy	22
18	F	52	25	Psychoneurosis, character disorder	Poor	Drank	1
19	F	43	25	Passive-aggressive personality	Fair	Did not contain anxiety	10
20	M	45	50	Schizophrenia, paranoid	Fair	Increased own dosage to 100 mg./day; improved	10

Except for the first one, who left treatment after two weeks, highly pleased with the results, these patients were continued on iproniazid therapy for from 5 to 13 weeks. Then, after newspaper publicity that the drug had caused one death in our city, anxiety was produced in both patients and medical staff, and for 10 weeks no new patients were given iproniazid. But patients with severe depression continued to be seen, and again the balance between the statistically remote chance of resultant hepatitis if patients received the drug and the apparently not so remote chance of suicide if it were not used changed in favor of the drug. Fifteen additional patients accordingly were given iproniazid treatment. However, the dose was reduced to either 50 or 25 mg. per day. Pyridoxine always was given concomitantly to minimize the possibility of peripheral neuritis.

Table 1, which presents data on these 20 patients, shows that the effectiveness of treatment with iproniazid seems to be reduced as soon as the starting dosage is reduced below 150 mg. per day.

The patients listed in table 1, all presenting a state of deep depression, were treated consecutively. The sex ratio of 10:10 was purely accidental. Since the ratio in the general patient load at our clinic is roughly three men to one woman, it would seem that depression occurs three times as frequently in women as in men, although the sample in this study is too small to warrant this conclusion. The patients' age range was from 35 to 67 years, with a mean of 44.5 and a median of 42. The duration of treatment was from 1 week to 40 weeks, with a mean of 9.8 and a median of 8.5.

The initial psychiatric diagnosis (see table 1) usually was made when the patient first arrived at the clinic. Where depression was not a major consideration at that time, the diagnosis indicates presenting symptoms, signs, and history; those who arrived in a depressed state are so diagnosed.

The effect of iproniazid is recorded as excellent if there was a total reversal of symptoms of depression, anorexia, insomnia, and others. A reversal of most of the symptoms, with amelioration of others, is considered good. A fair report means some amelioration of symptoms, but of insufficient degree to be good or excellent. Responses of those who obtained no effect from treatment with the drug are marked poor. In two of the four cases so reported (11 and 18) the patients resumed heavy drinking, and treatment was stopped as too dangerous for an irrational patient already using a hepatotoxic agent—alcohol. Also, iproniazid has been reported as a potentiator of alcohol and other depressants. The third poor result (case 10) was recorded for a patient whose medication was changed inadvertently at the end of two weeks, administration of iproniazid being stopped without a note of explanation in the chart. The fourth (case 14) was recorded after four weeks and shows the only true poor result in the series, possibly due to the low dosage schedule. However, one may consider that some success was obtained even from low dosages in that the disease did not progress toward suicide, as had seemed possible if not probable.

Table 2 shows the results of treatment by sex. If good results are combined with excellent, and fair with poor, the male and female groups are comparable. A slight shift toward better results in females, however, is perceptible.

Table 3 records results of iproniazid therapy according to dosage. Generally, better results were obtained when the initial dosage was the recommended 150 mg. per day. Of the eight persons with poor and fair responses, seven received 50 mg. or less per day. Since this series was completed, I have returned to use of the higher dosage range. As soon as good effects are seen, usually in about two weeks, doses are reduced as much as possible, to 50 or 75 mg. per day.

No side-effects were observed in the group reported here. One female patient had had pitting edema of the feet and ankles prior to the use of iproniazid; the edema was controlled by administration of acetazolamide (Diamox). Edema of the feet as a side-effect of iproniazid therapy has been reported. Might this not be a psychophysiological reaction fairly common in patients with an agitated depression, with or without treatment? If the edema is only a symptom of the general illness, it could be either unaffected, improved, or worsened by administration of a drug. Banghart[4] reported objective improvement of swollen joints, skin, and muscles in his study on patients with rheumatic diseases, and the development of facial edema during iproniazid treatment which receded on withdrawal of the drug. It clearly is difficult to assess this side-effect properly. All patients in this series were given polyvalent vitamins,[5] including pyridoxine, which may explain the absence of peripheral neuropathies. In no instance was dextro amphetamine sulfate given concomitantly with iproniazid, as suggested by Kline,[6] because of our experience with addiction-prone patients.

TABLE 2.—*Results of Iproniazid Therapy in Twenty Alcoholics*

	Patients, No.		
Results	Male	Female	Total
Excellent	1	5	6
Good	4	2	6
Fair	3	1	4
Poor	2	2	4

Comment

While the number of patients surveyed in this study is small, the series involves a problem not frequently seen in extreme severity. It would seem that the data are sufficient to conclude that administration of iproniazid is beneficial in cases of alcoholism when (1) history and physical examination show patients to be free from past or present serious liver involvement, (2) the drug is given with pyridoxine, (3) the risk of drug complications is much less than that of death or extensive hospitalization, and (4) the patients are not drinking. There were no cases of hepatitis or hepatic involvement seen in this series, nor did any peripheral neuritis develop after therapy was started. There were no suicides, and no patients were sent to a hospital, although two (cases 11 and 18) were lost to the study through further drinking.

TABLE 3.—*Effect of Dosage on Success of Iproniazid Therapy in Twenty Alcoholics*

	Daily Dosage			
Results	150 Mg.	100 Mg.	50 Mg.	25 Mg.
Excellent	3	1	1	1
Good	2	0	4	0
Fair	1	0	2	1
Poor	0	0	3	1

In this series iproniazid was more effective when given in initial dosages of 150 mg. per day. Results appear to demonstrate that iproniazid is of value in the treatment of the depression seen in alcoholic patients. It also seems to have helped these patients to refrain from continued use of alcohol as a cure for their depression. It is probable that the occurrence of suicide or hospitalization (and also just plain misery) has been reduced by the use of iproniazid in these patients. Since none of the patients recorded as showing a poor result from therapy is known to have been hospitalized for depression or to have committed suicide, the case selection may have erred on the side of overprotection, for, if these patients were truly suicidal but did not kill themselves after receiving no benefit from the treatment, one could assume them to be wrongly chosen. Perhaps enough benefit was obtained to prevent suicide. However, an important point in the therapy was that all patients were told the nature of their illness, that the pills were known to produce certain side-reactions making it necessary for us to keep close track of their progress, and generally that the aim in the treatment was to help them. This bit of psychotherapy may have been sufficient to turn the tide in some. However, since of the many patients whom we were unable to handle as outpatients, some did commit suicide and some needed hospitalization for long periods, I believe that this therapy of supportive relationship is inadequate to handle all such cases of severe depression. For these patients the question of suitable drug therapy should be considered. It is hoped that the new chemical analogues of iproniazid will be safe and more rapidly effective. One of these is currently being assayed clinically and will be reported on.

Summary

Twenty patients with severe depression, all alcoholics of long standing, were given iproniazid (Marsilid) phosphate in varying dosages. Sixteen obtained fair to excellent results from this treatment. All those chosen for this treatment were shown by history and gross physical examination to be free from liver disease. None developed liver disease, committed suicide, or had to be sent to a hospital, although two patients quickly resumed drinking. The results of this study indicate that the use of a high dosage increases the effectiveness of iproniazid.

150 Otis St. (3).

The iproniazid (Marsilid) phosphate used in this study was supplied by Hoffman-La Roche, Inc., Nutley, N. J.

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EVALUATION OF HUMAN FIBRINOLYSIN (ACTASE)

LACK OF FIBRINOLYTIC ACTIVITY AFTER INTRAVENOUS ADMINISTRATION IN MAN

Anthony P. Fletcher, M.D., Norma Alkjaersig, M.S., William D. Sawyer, M.D.
and
Sol Sherry, M.D., St. Louis

The effects of a preparation described as a human fibrinolysin were studied in vitro and in vivo to judge its possible usefulness in treating thromboembolic disease. The tests in vitro estimated the components of the plasminogen-plasmin and the coagulation system, and the results led to the expectation that the preparation would be ineffective as a thrombolytic agent in man. The tests in vivo consisted of the slow intravenous infusion of the preparation into six patients with various chronic diseases and the hourly determination thereafter of thrombolytic activity, plasma plasminogen and fibrinogen concentrations, and plasma euglobulin thrombolytic activity. The results yielded no evidence that the preparation enhanced the clot-dissolving ability of the plasma of patients.

Therapy for acute thromboembolic vascular disease has been only relatively satisfactory, and currently much attention is being devoted to its development. Among the newer approaches is one motivated by the novel concept that thrombi and emboli might be lysed in vivo by appropriate fibrinolytic enzyme therapy. The objective, with this form of therapy, is to impart to the circulating plasma a powerful clot-lysing ability which, when sustained for long enough periods, will effect the lysis of obstructing thrombi. The successful institution of such a controlled thrombolytic (clot-lysing) state in vivo, without hazard to the patient, could hold great promise for the therapy of thromboembolic vascular disease. (The term "thrombolysis" is used to designate a process by which preformed clots [or thrombi] are lysed. The adjective "thrombolytic" is used to describe biochemical moieties capable of producing thrombolysis. This nomenclature is clearly preferable to "fibrinolysis" and "fibrinolytic" because of ambiguities inherent in the latter terminology.)[1]

From the Department of Medicine, Washington University School of Medicine.

Investigators have favored different approaches toward the problem of inducing an in vivo thrombolytic state in man. Chief interest has focused on attempts to utilize the plasminogen-plasmin enzyme system because of its physiological role in the resolution of in vivo fibrinous deposits. Plasminogen or profibrinolysin is the naturally occurring, inactive precursor of plasmin or fibrinolysin, a proteolytic enzyme whose spectrum of activity generally is similar to, though less intense than, that of trypsin. Although, at first glance, plasmin would appear to be a most suitable agent for thrombolytic therapy, there are at least three serious disadvantages to its use. 1. Plasmin dissolves preformed clots at a slow rate. 2. Large amounts of plasmin can be rapidly inactivated by the powerful antiplasmin content of the circulating plasma. 3. Plasmin, given in large enough amounts to sustain an increased proteolytic activity in the circulating plasma, will accelerate the digestion of a variety of proteins, particularly those connected with the coagulation mechanism, and lead to a serious hemorrhagic diathesis.

Recent studies have indicated that there is a much more sensitive mechanism for thrombolysis than had been suspected. Although it had been known for some time that plasminogen is a significant component of all thrombi, being incorporated within the clot, it has only recently been recognized that the major and most rapid mechanism for clot dissolution involves the activation of plasminogen to plasmin within the interstices of the thrombus itself. This activation of clot plasminogen is mediated by a plasminogen activator, which diffuses from the circulating plasma into the thrombus. As a consequence, the clot-lysing ability of the plasma may be equated with its activator content, a view supported by the experimental evidence.[1] The use of plasminogen activators as thrombolytic agents surmounts the difficulties encountered with plasmin, since (1) it simulates the natural mechanism for rapid fibrin resolution, (2) it can operate relatively independently of circulating plasmin inhibitors, and (3) it can produce clot dissolution without increasing the general proteolytic activity of the plasma, with its attendant hazard of increased proteolysis. Thus, though some have advocated the use of plasminogen activators and others have used plasmin preparations, cogent biochemical and physiological reasons exist for preferring the use of plasminogen activators and for avoiding the use of plasmin (fibrinolysin).[1]

Regardless of approach, the basic need in the development of thrombolytic therapy is for a nontoxic agent capable of inducing and sustaining a marked, measurable, and controlled increase in the clot-dissolving capacity of the plasma. The introduction of any therapeutic agent for this purpose should be accompanied by the demonstration, in the patient, that enhanced plasma thrombolytic activity follows its administration. The fact that this objective may not be readily achieved by all fibrinolytic agents introduced for clinical use is illustrated by our studies with a preparation designated by the manufacturer as "human fibrinolysin" (Actase). This preparation recently has become commercially available and has excited considerable clinical interest.[2] Unfortunately, the assay procedure performed for its standardization is one requiring a fibrinolytic test system of an empirical and undefined nature. Such an assay procedure, although useful to the manufacturer, does not provide meaningful data for physicians interested in inducing and sustaining an active thrombolytic state in vivo. The induction of such a state requires data as to the separate concentrations of plasminogen activator and proteolytic enzyme present in the preparation to be used, and these data should be expressed in meaningful biochemical terms.

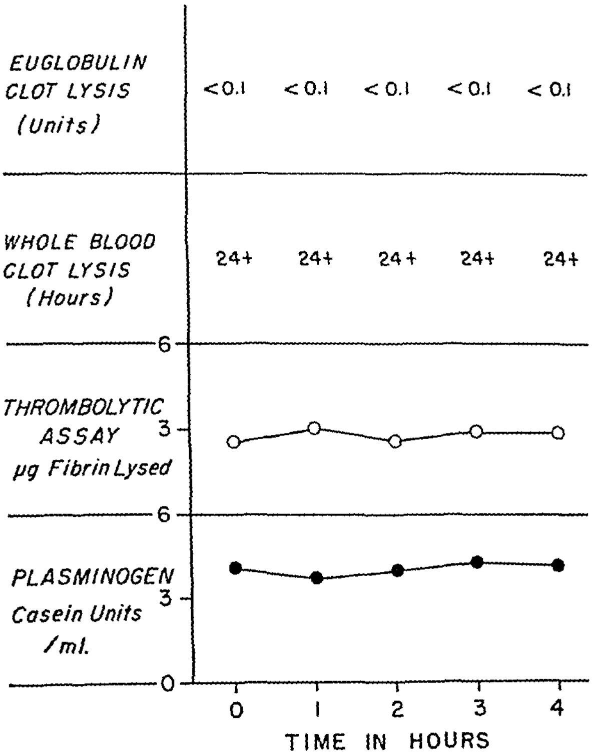
Therefore, in our studies with the human fibrinolysin we determined its composition in terms of its activator and plasmin content. On this basis, we could predict the in vivo thrombolytic activity which might be expected from its infusion[3] and then tested the validity of this prediction by infusion of this preparation (in the recommended dosage) into man. The results demonstrated that it had a composition other than that stated by the manufacturer; that, on the basis of our analysis, we could predict that its infusion into man would fail to produce specific detectable enzymatic change; and that decisive confirmation of its ineffectiveness as a thrombolytic agent was obtained by direct investigation in man.

Materials and Methods

Two different lots of the experimental substance were purchased through retail sources; samples from each lot were used for laboratory assay and then tested in patients. The methods used for assay for components of the plasminogen-plasmin and the coagulation system were as previously described.[1] The method for measurement of plasma thrombolytic activity involved assay of radioactivity released from an isotopically labeled, preformed clot which was immersed in the patient's plasma. This method provides a direct estimate of the clot (thrombus)-lysing power of plasma, and it has been refined to a sufficient state of sensitivity to allow detection of thrombolytic activity in plasma obtained from healthy, stress-free persons.[4] Physiologically relevant data are obtained, and the validity of the method is well established. Streptokinase (the plasminogen activator used in the preparation of the human fibrinolysin) was assayed by titration against specific antibody; a fibrinolytic indicator system was used, and the accuracy of the method was within ±10% limits, since a comparison of regression slopes was used in the procedure.

Results

Analysis of the product revealed the presence of both activator and plasmin. Evidence that the experimental substance was contaminated with substantial amounts of plasminogen activator (the manufacturer claims that all the streptokinase originally used is later removed) was provided by the demonstration that it readily activated bovine plasminogen, a phenomenon which could not be attributed to the enzyme, plasmin.



Effect of infusion of 50,000 fibrinolytic units of human fibrinolysin over two-hour period in 63-year-old man. No change in fibrinolytic moieties was detected.

Triplicate assays for streptokinase and plasmin were made on one vial (containing 50,000 fibrinolytic units) from each lot. One vial from the first lot contained 5.1 casein units of plasmin and 6,500 units of streptokinase. A vial from the second lot contained 3.5 casein units of plasmin and 6,750 units of streptokinase. Buffer salts were estimated to constitute 90 to 95% of the vial contents. The accuracy of the assay procedure was confirmed by mixing 5 units of human plasmin (prepared in this laboratory) with 6,500 units of streptokinase. This mixture of plasmin and streptokinase was shown to possess identical biochemical activity with regard to proteolytic and plasminogen activator assays. Thus, one vial of the human fibrinolysin contains a minute quantity of plasmin (equivalent to the quantity of plasminogen extractable from 2 ml. of plasma) and a small quantity of streptokinase.

Such in vitro assay evidence suggested that the infusion of the preparation into man (with use of the recommended doses of one or two vials) would fail to exert any detectable biochemical effect. First, the infusion of 5 to 10 plasmin units over a two-hour period into a circulatory reservoir containing 10,000 to 20,000 antiplasmin inhibitor units is unlikely to lead to any detectable biochemical change. Second, the infusion of 6,500 to 13,000 units of streptokinase over a similar period and into a circulatory reservoir containing 9,000 to 6,000,000 units of antibody (depending on the patient's state of immunization) also will prove to be unrewarding. Were there evidence that the components of the mixture exerted synergistic effects in man, such simple calculations would be invalid, but evidence of this nature is wholly lacking.

Infusion in Man.—Six patients, suffering from diverse medical conditions of a chronic nature, each received a single infusion. Four patients received 50,000 fibrinolytic units, and two received 100,000 units of fibrinolysin. The infusions were administered over a two-hour period, as recommended by the manufacturer, and blood samples for analysis were withdrawn before, during, at the termination of, and for two hours after the infusion.

The procedure used and the results obtained in a single patient are illustrated in the figure. The more important assay results obtained for the whole group are presented in the table. As is obvious from inspection of table and figure, the infusion failed to influence plasma thrombolytic activity, plasma fibrinogen or plasminogen concentrations, or the lysis time of the euglobulin precipitate. Moreover, one-stage prothrombin times, whole blood clot-lysis times, and assays for plasma antithrombin activity likewise were unaltered by the infusion. Statistical testing confirmed the impression gained by inspection, since all differences were nonsignificant ($p > 0.1$ in each instance).

Serial Observations on Fibrinolytic Moieties Before, During, and After Infusion of Human Fibrinolysin.[*]

Time, Hr.	Thrombolytic Assay, μg Fibrin Lysed	Plasma Plasminogen, Casein Units/Ml.	Plasma Euglobulin Clot Lysis, Units	Fibrinogen, Mg./100 Ml.
0	2.8±1.0	3.5±0.7	<0.1	363±126
1	3.6±1.9	3.4±0.9	<0.1	342±145
2	3.4±1.5	3.7±0.8	<0.1	315±143
3	2.8±0.4	3.5±0.8	<0.1	385±160
4	2.7±0.5	3.6±0.7	<0.1	361±142

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[*] Control specimen taken at 0 hr. Infusion period (100,000 or 50,000 units of Actase) extended from 0 to 2 hr. Mean and standard deviation of the group observations displayed; all differences not significant ($p > 0.1$).

Since the human fibrinolysin is known to produce pyrogenic effects in man,[2] the patients received aspirin prior to, and at the end of, the infusion period. Despite this precaution, three of the six patients developed chills and mild fever (with temperatures up to 101 F [38.3 C]) four to six hours later.

Comment

The attainment of control over thrombus dissolution in the vascular system would represent a major therapeutic advance. Of the many key therapeutic problems still unsolved, the control of plasma thrombolytic activity itself would seem to be the one most immediately susceptible of solution. The conceptual basis, in biochemical terms, has been most nearly accomplished, and, although practical difficulties remain, measurement parameters have been developed and a physiological approach devised.[1] Consequently, the introduction of a material such as human fibrinolysin into therapeutic use is a cause for disappointment.

We are satisfied, after review of the expanding literature on this product, that the evidence indicates that the clot-dissolving ability of the plasma has not been enhanced by the infusion of the product into patients. The meager and unsatisfactory data,[5] purporting to demonstrate such enzymatic effects, all were obtained one or more hours after the termination of the infusion, at which time the well-recognized phenomenon of plasminogen activator release secondary to any nonspecific pyrogenic response could well account for these observations. The results of the present investigation clearly indicate that, in patients, this human fibrinolysin is impotent as a clot-dissolving agent, because, in the doses recommended, it failed to increase the thrombolytic activity of the plasma. This lack of effect could have been predicted readily from a knowledge of the products composition; there is too little streptokinase or plasmin present to exceed the available antistreptokinase and antiplasmin levels of the circulating plasma. It seems reasonable to ascribe any clinical effects attributable to this agent to mechanisms other than clot dissolution.

The desire for a thrombolytic agent which can be used simply is so great that there has been reluctance to recognize the ability of the organism to inhibit these agents. The in vivo activity of all "fibrinolytic enzyme" preparations (regardless of designation) which currently are being made available by pharmaceutic firms in the United States for investigation in patients as thrombolytic agents, can be shown to depend for the most part, if not completely, on their streptokinase content. Proper use of such preparations requires knowledge of the antistreptokinase content of the plasma; this level, which may vary as much as a thousandfold among subjects, must be significantly exceeded before any thrombolytic activity can be induced in the patient. A simple test has been developed to determine how much of the preparation will be required in each case to induce such an effect. The dose required to sustain the effect may then be predicted from previous studies on the rate of clearance of streptokinase from the circulation.[3]

Summary

The aim in the development of fibrinolytic agents for the therapy of thromboembolic disease is to induce in the plasma of patients an enhanced thrombolytic activity which can be sustained, without hazard, for long enough periods to effect the resolution of obstructing thrombi. Recent evidence indicates that this desired state can be more readily accomplished with plasminogen activators than with plasmin (fibrinolysin). That fibrinolytic agents introduced for clinical use may not prove active in vivo is illustrated by studies on human fibrinolysin (Actase). This preparation, in the recommended dose, failed to enhance the clot-dissolving ability of the plasma of patients. Analysis of samples of this product revealed that each vial contained small quantities of streptokinase and human plasmin in amounts insufficient to produce any significant thrombolytic activity in vivo.

600 S. Kingshighway (10) (Dr. Fletcher).

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SUBUNGUAL HEMORRHAGE IN PAN WASHERS

Peter I. Long Jr., Dayton, Ohio

The purpose of this study was to determine the factors involved in an occupational affliction of kitchen workers, namely a soreness of fingers with extravasion of blood under the finger nail. Forty volunteer subjects scrubbed pans under standard conditions with a variety of detergents, and comparisons were made between one hand which was bare and the other hand which was gloved, a small amount of the detergent solution being placed in each glove. A typical subungual hemorrhage with soreness was produced in the gloved hand of one subject. At its height the lesion resembled a traumatic hematoma. Eczematoid dermatitis occurred in six subjects but involved both gloved and ungloved hands in every case. No differences were found among the detergents used. Gloves should be worn for prolonged, repeated pan washing, and the washing solution should not be allowed to accumulate inside the gloves.

After the report of three cases of subungual hemorrhages which occurred among the pan washers at the Veterans Administration Center, Dayton, Ohio,[1] a series of clinical studies were formulated and carried out, which, it was hoped, would further elucidate the pathogenesis of these lesions. From the original studies it was felt that the primary etiological factors were the pH of the washing solution trapped inside the washers' gloves and the trauma of scrubbing.

Method

The study was conducted with a group of 40 volunteers from the domiciliary section of the center. The subjects were men between 46 and 70 years of age. About one-third of the subjects were Negroid. Each member of the group was patch-tested for sensitivity to detergent and rubber prior to the beginning of the study. None of the men of the group demonstrated any sensitivity after 24 or 48 hours when the patches were removed.

The men were then divided into groups of five, and each group was assigned a specific cleaning agent and washing procedure. Each man wore a rubber glove on one hand and kept the other hand bare. Each glove was kept filled with a small amount of the washing solution used. In all experiments the water temperature was maintained between 100 and 112 F. The pH was kept between 7.2 and 9. To simulate actual pan room scrubbing conditions as nearly as possible, it was decided to have the men scrub on corrugated metal boards, so small washboards were used. Several times each day the boards were coated with sugar which was heat-melted on the metal. This gave the men something to clean and made effort requisite, causing trauma to the hands. The men were constantly observed and required to scrub for about equal periods of time with the gloved and ungloved hand. The scrubbing was done with standard gauge steel wool obtained from the kitchen. Each group scrubbed for three hours a day for a total of 10 days, Saturday and Sunday being omitted. Photographs of each man's hands and nails were taken before and at the conclusion of the study. All specific lesions developing on the hands or under the nails were photographed immediately when noted.

Washing solutions assigned to each five-man group were as follows: group 1, liquid detergent 1; group 2, liquid detergent 2; group 3, powdered detergent 1; group 4, powdered detergent 2 (a product being used in the hospital); group 5, powdered detergent 1 and pan drippings; group 6, powdered detergent 2 and pan drippings; group 7, pan drippings; and group 8, water (control).

Water was added to each substance tested as a dilutant. The detergents were diluted according to instructions given by the manufacturer for the various products.

The pH of the glove solution varied from 7.2 to 7.6 in this series. In none of our experiments were we able to reduplicate the acid condition of the solution trapped in the gloves of the pan washers in the hospital kitchen which ranged in pH from 4.5 to 7. All types of skin lesions, as well as nail bed pathology, were recorded. Hands were examined each day at the beginning and at the end of the three-hour period of scrubbing.

One substance, a powdered detergent, composed of sodium sulfate and alkyl arylsulfonate, was injected by hypodermic needle beneath my own nails in the following manner. A 22-gauge needle was slowly inserted beneath the nail, bevel down, to a depth of 0.25 in., and about 0.1 to 0.3 cc. of test solution was injected. Every attempt was made to make this as atraumatic as possible.

The following test solutions were prepared from this detergent and injected: (1) sodium sulfate; (2) the detergent (composed of sodium sulfate and alkyl arylsulfonate) in water; (3) sodium sulfate and grease; and (4) alkyl arylsulfonate and grease. Additional tests performed one month later involved solutions of sodium sulfate and alkyl arylsulfonate heated to 110 F. These solutions were injected into the first and second fingers of the left

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From the Dermatology Section, Brown General Hospital, Veterans Administration Center.

hand. No other direct subungual inoculations were attempted, since we were unable to obtain volunteers who would submit to the injection.

Results

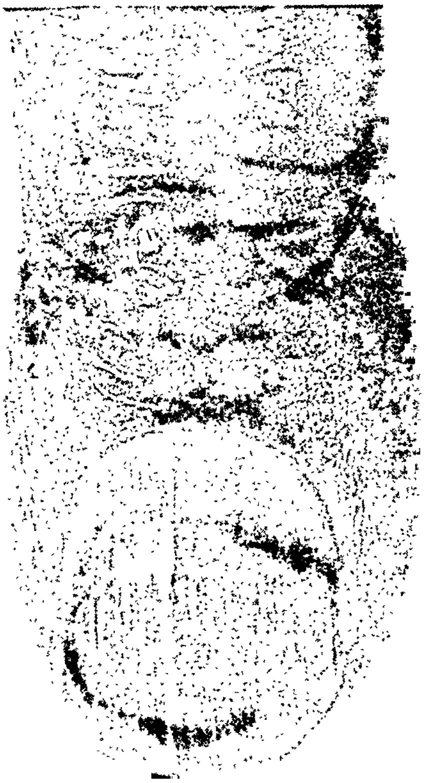
During the course of this study, we reproduced, under controlled conditions, one typical subungual hemorrhage, as described in the original report.[1] The case is reported here in detail. Four types of reaction of the skin of the hands were noted during this experiment—dryness, maceration, dyshidrosis, and eczema. Every subject exhibited maceration of the skin of both hands, usually slightly worse on the gloved hand. Each day this subsided within several hours after the scrubbing was stopped. There was a slight drying and cracking of the skin in practically all subjects, but it was not considered disabling. There were six cases of eczematoid dermatitis, three of which were severe enough to warrant the removal of the men from the experiment. In each instance both the gloved and ungloved hands were involved. The men presented erythema, vesicle formation, and weeping lesions, which appeared first on the fingers and then spread to the dorsum of the hands. In none of these cases were the nail beds involved.

One case was classified as dyshidrosis. The subject developed small multiple white papules on both hands, on the dorsal as well as the ventral surfaces. These would disappear within two hours after the subject ceased scrubbing. They could be reproduced by merely soaking the hands in water for two hours at a temperature of 90 F. Subungual injection of the test substances described above did not produce any significant lesions in one subject.

Report of a Case

A 70-year-old man was placed in group 5 to scrub with a solution that consisted of powdered detergent, water, and pan drippings. He scrubbed on a corrugated board. The right hand was gloved and the left hand was ungloved. The water temperature was 110 F, and the pH ranged from 7.2 to 7.6. The subject's general health was good. He never had had skin disease or any disease involving the hands or nails.

On the second day of exposure, the subject complained of soreness under the nail of the third finger of the gloved hand. On examination at this time there was a blush on the distal one-third of the nail bed, and it was tender on pressure. There was no evidence of laceration or separation of the nail from the nail bed. At the end of scrubbing on the third day a small bluish colored area, about 5 mm. in diameter, was noted on the lateral portion of the nail bed, two-thirds the distance from the nail base. On the fourth day the man continued to scrub; however, he complained of soreness and had to guard the finger while scrubbing. On examination, the distal one-third of the nail bed was tender to pressure and red in appearance. Since the next days were Saturday and Sunday, no scrubbing was done. However, on Monday, prior to his beginning to scrub, the man's finger presented a typical picture of the subungual hemorrhages previously described. The nail bed was fiery red, and multiple small, punctate, dark, hemorrhagic areas were scattered throughout. The man was stopped from participating in the experiment but was examined daily. The bleeding points coalesced, and in several more days the finger showed the appearance of a traumatic hematoma of the nail. In about one month's time the distal one-third of the nail had separated from the nail bed and was removed. Four months later the nail had not recovered the distal one-third of the nail bed. This man would not permit subungual injection by hypodermic of the component substances of the solution in which he was scrubbing.



Maximum extent of fingernail lesion in subject in case 1.

Comment

One case of subungual hemorrhage was produced in 40 attempts and occurred under conditions which simulated the actual conditions in a pan washing room. This hemorrhage occurred on the gloved hand. The glove contained a mixture of warm water, a powdered detergent, and kitchen grease. It occurred under conditions conducive to trauma and developed within three days after exposure. The pH of the solutions seemed unimportant since in this instance the pH of the glove and the pan solution remained equal, varying from 7.2 to 7.6. The subungual injection of the component parts of the detergent and solution in which this man scrubbed did not produce subungual hemorrhage in another subject.

From the experiments described, the mechanism of these hemorrhages may be explained as follows. The washing solution trapped in the gloves softens the skin and subungual tissue, and the trauma of scrubbing probably causes small breaks between the nail and the nail bed. The detergent solution and grease is forced into the subungual tissue by pressure on the water trapped inside the glove. These substances then produce hemorrhage in the subungual tissue in a susceptible person. Trauma alone cannot account for the changes observed, since the lesions progressed after the person was removed from the source of trauma.

Summary and Conclusions

Forty volunteers were subjected to experiments planned to produce subungual hemorrhages. A subungual hemorrhage was successfully produced in one subject under conditions simulating those found in actual pan scrubbing. Clinically, the lesion described progressed from erythema to hemorrhage and at its peak had the appearance of a traumatic hematoma.

No specific etiological agent was identified. Injections of suspected substances subsequently produced no hemorrhages in one subject. In these experiments there resulted six cases of eczematoid reaction of the hands, half of which were considered disabling.

Pan washers should wear long, cuffed, watertight gloves to prevent the accumulation of washing solution in contact with skin surfaces.

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TREATMENT OF MALIGNANT PLEURAL EFFUSIONS BY TALC POUDRAGE

George J. Haupt, M.D., Rudolph C. Camishion, M.D., John Y. Templeton III, M.D.
and
John H. Gibbon Jr., M.D., Philadelphia

The operation of talc poudrage here described is designed to stop persistent pleural effusions in cases of incurable cancer. The incision permits exploration of the affected hemithorax and can be extended if the lesion is found to be resectable. If it is not resectable, the pleural surfaces are generously dusted with sterile talc (USP) and two fenestrated intercostal drainage tubes are inserted through separate stab wounds; the latter permit application of suction to maintain complete obliteration of the pleural space for 48 to 72 hours. Two cases are described in detail, and the results of 19 operations are described. Thirteen were for primary pulmonary neoplasms; three were for metastatic carcinoma of the breast. In every instance dyspnea was relieved and recurrence of the effusion was prevented. There were no complications or deaths attributable to the operation.

The treatment of persistent pleural effusion due to incurable cancer is a difficult problem. The effusion is usually due to involvement of the pleura by the neoplastic process, but it may result from extensive lymphatic obstruction or inflammatory reaction secondary to a tumor within the lung. Dyspnea may be severe; it results from compression of the ipsilateral lung by the fluid and the contralateral lung by shift of the mediastinum. The pleural fluid contains not only electrolytes but proteins, leukocytes, and a varying concentration of erythrocytes. Early recurrence of the effusion after aspiration usually necessitates increasingly frequent thoracenteses, which debilitate the patient.

A variety of techniques for obliteration of the pleural space have been proposed. In 1906, Spengler[1] instilled silver nitrate into the pleural space of patients with spontaneous pneumothorax of tuberculous origin. He later used glucose to induce obliterative pleuritis.[2] The introduction of other irritating substances for the purpose of producing pleural symphysis has also been reported.[3] Parietal

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From the Department of Surgery, Jefferson Medical College. During this study Dr. Camishion was a trainee of the National Cancer Institute, Public Health Service.

pleurectomy as a method of producing permanent pleural symphysis was described by Gaensler[4] and later by Thomas and Gebauer[5] for the treatment of recurrent and chronic pneumothorax. The instillation of radioactive gold colloid has been advocated for the treatment of malignant pleural effusions. It is effective in preventing recurrence of the effusion in only 30 to 50% of patients.[6]

In 1935, Bethune[7] first reported the use of talc poudrage as a preliminary procedure to lobectomy. Medici[8] and later Meade and Blades[9] and Smith[10] reported the use of this method in the treatment of recurrent and chronic pneumothorax. Pulmonary function studies made after obliteration of the pleural space by talc poudrage have been reported by Paul and others[11] and Knowles and others.[12] No permanent ventilatory impairment was demonstrated.

The purpose of this paper is to describe the results obtained from the use of talc poudrage in the treatment of 19 patients with pleural effusion secondary to irremovable cancer. The procedure was well tolerated and attended with no significant morbidity. Dyspnea is not a contraindication, since the prevention of the effusion improves ventilation. Biopsy can be done at the time of operation. It is immaterial whether the malignant process is one arising from a primary intrathoracic tumor or whether it has resulted from pleural involvement secondary to a neoplasm originating outside of the thorax.

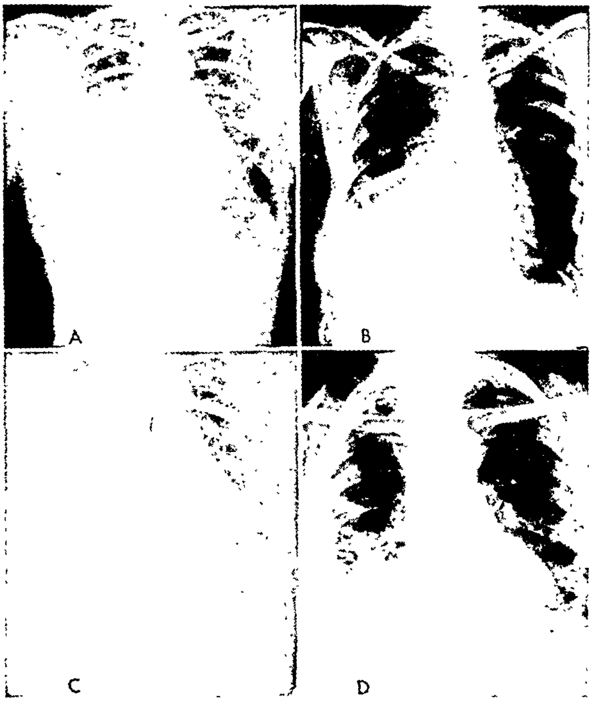
Technique and Procedure

With the patient lying on his side under light endotracheal anesthesia an oblique incision, 4 to 10 cm. in length, is made in the infra-axillary region. The pleural space is entered through the bed of a short segment of resected rib or through an interspace, usually the sixth or seventh. All free and loculated fluid is removed and exploration is carried out. The presence of noncontiguous pleural metastasis or other indications of nonresectability can be established quickly and a biopsy sample for frozen section can be taken. Should the lesion prove to be resectable, the incision may be extended and converted into a standard posterolateral thoracotomy. When nonresectability is established, the pleural surfaces are generously dusted with sterile talc (USP) and two fenestrated intercostal drainage tubes are inserted through separate stab wounds into the pleural space. The lung is gently inflated under direct vision. In some instances, it is necessary to decorticate an area of the underlying lung to permit complete obliteration of the pleural space. The incision is closed and sufficient suction is applied to the drainage tubes for 48 to 72 hours to insure complete obliteration of the pleural space.

Report of Cases.—The following two brief case reports are presented as examples of the application of this procedure. One patient had pleural effusion secondary to metastatic carcinoma of the breast and the second had effusion due to bronchogenic carcinoma.

CASE 1.—A 30-year-old woman was admitted to Jefferson Medical College Hospital on Dec. 22, 1956. She complained of progressively severe dyspnea of two months' duration. Two years previously a simple mastectomy on the left had been performed for medullary carcinoma of the breast.

A right pleural effusion was present (see figure, *A*), from which 800 ml. of straw-colored fluid was aspirated. No acid-fast bacilli or neoplastic cells were found. After thoracentesis, x-ray examination of the chest revealed no lesion of the lungs. Bronchoscopic examination was negative. On Dec. 27, 1956, the right pleural space was explored through a small incision and about 1 liter of straw-colored fluid was removed. Many pleural nodules of anaplastic carcinoma were present. Talc poudrage was carried out, as previously described. The intercostal drainage tubes were connected to a source of negative pressure for 48 hours. The patient's postoperative course was uneventful and she was discharged from the hospital on the eighth postoperative day, free of symptoms. She survived for four months without dyspnea or recurrence of the pleural effusion (see figure, *B*).



Top (case 1), *A*, preoperative roentgenogram of chest made Dec. 22, 1956; *B*, postoperative roentgenogram of chest made Jan. 4, 1957, showing improvement. *Bottom* (case 7), *C*, preoperative roentgenogram of chest made July 30, 1957; *D*, postoperative roentgenogram of chest made Aug. 20, 1957, showing improvement.

Case 7.—A 67-year-old man was admitted to Jefferson Medical College Hospital on July 30, 1957, with the chief complaint of dyspnea. He had lost 50 lb. (22.7 kg.) in weight during the previous three months. A massive pleural effusion was present on the right (see figure, *C*). On Aug. 1, 1957, 4 liters of bloody fluid was removed. No neoplastic cells or acid-fast bacilli were found and bronchoscopic examination showed normal findings. Thoracenteses on Aug. 6 and again on Aug. 12 were productive of 2,500 ml. and 2,100 ml., respectively, of bloody fluid. A histological diagnosis could not be established, and his condition was steadily deteriorating. On Aug. 16, 1957, with the patient under light endotracheal anesthesia, the right pleural space was explored through a small incision and 2,500 ml. of bloody fluid was removed. Both the visceral and the parietal pleura were found to be studded with nodules. Frozen section of one of the nodules was reported as "poorly differentiated carcinoma involving the pleura." Talc poudrage was performed, intercostal drainage was established, and the lung was reinflated. The intercostal drainage tubes were removed on the second postoperative day. The patient was discharged on the eighth postoperative day. There was no recurrence of dyspnea or of pleural effusion during the remaining 13 months of his life (see figure, *D*).

Results

Nineteen consecutive patients with persistent pleural effusion resulting from primary or metastatic intrathoracic cancer have been treated by talc poudrage (see table). The relief of dyspnea, prevention of recurrent accumulations of fluid, and palliation afforded have been striking. There was no operative mortality and no operative complications occurred. The average hospital stay was 10 days. Of the 19 patients 11 were men. Ten had primary carcinoma of the lung and one had a malignant mesothelioma. In six of the eight women the primary tumor was extrathoracic. Two women had primary carcinoma of the lung. The progress of all patients has been followed to the time of writing or until death. The longest period of follow-up is 26 months. There has been no recurrence of the pleural effusion in any case. Of the 19 patients 5 are living, at the time of writing, from 1 to 26 months after operation. Of the 19 patients 14 have died of their primary disease. The survival time of these patients ranged from 2 to 13 months, with an average of 6 months. All patients were relieved of their preoperative dyspnea.

*Summary of Case Data in Nineteen Patients Treated by Talc Poudrage**

				Operation		
No.	Age, Yr.	Sex	Diagnosis	Date	Type	Survival Time, Mo.
1	30	F	Metastatic carcinoma of breast with right pleural effusion	12-27-56	Right talc poudrage	4
2	59	F	Carcinoma of left lung with left pleural effusion	5-24-57	Left talc poudrage	13
3	57	F	Metastatic carcinoma of breast with left pleural effusion	6-29-57	Left talc poudrage	6
4	53	M	Carcinoma of left lung with left pleural effusion	7-3-57	Left talc poudrage	6
5	66	M	Carcinoma of right lung with right pleural effusion	7-21-57	Right talc poudrage	2
6	61	F	Metastatic hypernephroma with right pleural effusion	7-31-57	Right talc poudrage	26†
7	67	M	Carcinoma of right lung with right pleural effusion	8-16-57	Right talc poudrage	13
8	52	M	Carcinoma of right lung with right pleural effusion	8-22-57	Right talc poudrage	10
9	56	M	Anaplastic carcinoma of right lung with right pleural effusion	12-9-57	Right talc poudrage	2
10	72	M	Carcinoma of right lung with right pleural effusion	12-11-57	Right talc poudrage	3
11	63	M	Carcinoma of right lung with right pleural effusion	12-31-57	Right talc poudrage	2
12	59	M	Carcinoma of left lung	4-25-58	Left talc poudrage	8
13	64	F	Metastatic malignant thymoma with right pleural effusion	5-5-58	Right talc poudrage	5
14	55	M	Carcinoma of right lung with right pleural effusion	6-16-58	Right talc poudrage	3
15	65	F	Metastatic carcinoma of breast with right pleural effusion	8-12-58	Decortication and right talc poudrage	2
16	48	M	Anaplastic carcinoma of right lung with right pleural effusion	8-22-58	Right talc poudrage	12†
17	37	F	Carcinoma of right lung with right pleural effusion	11-12-58	Right talc poudrage	9†
18	51	F	Metastatic rhabdomyosarcoma with right bronchopleural fistula, empyema, trapped lung	6-12-59	Right lower lobectomy; decortication, right upper and middle lobes; talc poudrage	2†
19	60	M	Malignant mesothelioma with right pleural effusion	7-13-59	Right talc poudrage	1†

* There were no recurrent effusions in the series

† Living at time of writing (Aug. 15, 1959).

Summary

In 19 patients with persistent pleural effusion due to cancer, talc poudrage prevented recurrence of the effusion in every instance. No deaths and no complications were attributable to the operation. Gratifying relief of dyspnea was obtained in every case.

1025 Walnut St. (7) (Dr. Haupt).

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INITIAL CLINICAL REACTION TO THERAPEUTIC WHOLE-BODY ROENTGEN RADIATION

SOME CIVIL DEFENSE CONSIDERATIONS

William C. Levin, M.D., Martin Schneider, M.D., Galveston, Texas
and
Herbert B. Gerstner, M.D., San Antonio, Texas

The effects of whole-body roentgen radiation were studied in 11 patients with far-advanced neoplastic disease in order to form a picture of the typical initial response to ionizing radiations. The nominal air dose was 150 r in seven patients and 200 r in four. At this dosage level the duration of the latent period and intensity of ensuing symptoms were determined more by personal differences than by amount of radiation. During the "delay period" of one or two hours there were no symptoms. Two patients later experienced nausea, and two others remained asymptomatic. In the remaining seven, fatigue and apathy appeared abruptly from one hour to four and one-half hours after the irradiation. The onset of vomiting sharply marked the beginning of the initial reaction, which reached its climax five to eight hours after irradiation and then steadily receded. Evidently, among large groups of people exposed to radiation from a nuclear weapon, many who are capable of self-help during the first hour will become prostrated during the three hours that follow.

Medical application of Roentgen's discovery of the "x-rays" soon led to the observation that cancericidal doses of the new agent frequently elicited an early systemic reaction characterized by dizziness, fatigue, anorexia, nausea, and vomiting. This clinical complex—termed "radiation sickness"—developed into a more and more serious problem as the intensity and penetration of therapeutic radiation increased with the technical advancement of x-ray equipment.[1] The radiotherapist then learned to minimize the irksome side-effects by dividing the total dose into fractions delivered at intervals; the size of each fraction and the length of intervals between exposures were determined by the patient's disease and general condition. This procedure, together with closer restriction of radiation to the tissue volume intended for treatment, proved so effective that radiation sickness lost its significance for modern radiotherapy.

Renewed interest in the early clinical reaction, however, arose with the advent of the atomic age. Ever-accelerating use of nuclear energy, for military and industrial purposes alike, created the hazard of deliberate or, to a lesser degree, of accidental disasters exposing large populations to significant amounts of penetrating radiation. Under these

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From the departments of internal medicine and radiology, University of Texas Medical Branch, Galveston; and the Department of Radiobiology, School of Aviation Medicine (AU), Brooks Air Force Base.

circumstances, the early clinical sequelae that constitute the initial reaction to such exposure have left the realm of radiotherapy and have entered a sphere of concern to all physicians who, in an emergency, might be confronted with radiation casualties. This atomic age also brought about the need for more precise terminology, based on the time relationship between the various phases in the clinical response to penetrating radiation. To specify the early burst of signs and symptoms, the broad term radiation sickness should be replaced by the more restricted and more striking denotations "initial" or "prodromal" reaction.[2]

Although it has been almost eliminated as a complication of routine therapy, the initial reaction still can be seen and studied in the rare patients who require treatment with single high doses to the entire body.[3] Observations on such patients merit particular interest because they are the only human samples for whom type of radiation, dose distribution, and total dose are known with certainty; therefore, they are indispensable for establishing correlations between physical parameters and the clinical consequences of radiation. On the basis of 11 case histories, the present report describes the early radiation-induced response and evaluates its potential role in nuclear disasters.

TABLE 1.—*Data on Patients Treated with Whole-Body Roentgen Radiation*

Patient, No.	Sex	Age, Yr.	Diagnosis	Nominal Air Dose, r	Start of Radiation; Time of Day
1	F	62	Hodgkin's disease	150	0915
2	M	57	Adenocarcinoma	150	1235
3	F	61	Hodgkin's disease	150	1115
4	M	39	Hodgkin's disease	150	0930
5	M	69	Giant follicle lymphoma	150	1200
6	F	15	Ewing's sarcoma	150	1310
7	M	5	Acute lymphocytic leukemia	150	0930
8	M	48	Carcinoma of kidney	200	1010
9	M	13	Malignant lymphoma	200	0900
10	M	25	Lymphosarcoma	200	0930
11	M	52	Malignant lymphoma	200	0900

Method

Previous studies[4] had shown that whole-body irradiation might be a tool for inducing palliation, or even temporary remission, in patients with cancer inaccessible to more promising kinds of treatment. Accordingly, the 11 patients selected for the present series suffered from malignant neoplasms that were so widely disseminated and so far advanced—predominantly stage 3 lymphomas of various histological types (table 1)—that any other mode of management appeared hopeless. The antecedent clinical history varied; in most instances, records revealed futile attempts at controlling the disease by local roentgen radiation, by steroid administration, or by chemotherapy.

Hospital admission preceded irradiation by at least one week; during this period each patient was seen daily by the same resident physician who, in addition to the usual examinations, recorded activity, behavior, and mental attitude. Seven of the patients were in relatively good general condition; they had permission to walk freely about the ward and to participate in moderate physical activities. For the remaining four, however, confinement to bed was necessary because of weakness, weight loss, and a tendency toward nausea and temperature elevation. The one-week adaptation phase was followed by the radiation treatment and then by a postexposure period of observation usually exceeding 10 days. At all times, even on the day of treatment, the initially established routine was maintained—examination by the same physician, normal meal schedule, and liberty of movement for ambulant patients. Administration of radiation, as a rule, occurred during the interval between breakfast and lunch (table 1); only occasionally did antiemetic treatment appear indicated.

The radiation source was a conventional roentgen ray apparatus operated under the following conditions: 250 kvp; 30 ma.; filtration added to beryllium window of tube, 1 mm. aluminum and 0.5 mm. copper; half-value layer, 1.2 mm. copper; open portal; and distance from target to midcoronal plane of the patient, 200 cm. At that distance, the dose rate in air averaged 9 r per minute. Multiplication of this value by exposure time yielded the "nominal air dose"[5] that was adopted for dosimetry throughout this analysis. As verified by radiographic check-films, the entire body remained well within the primary beam directed horizontally toward the patient who, with hips and knees flexed, lay on his side on a treatment table. First, facing the x-ray machine, each received one-half of the prescribed dose; then, presenting their posterior aspects to the source, they received the remaining half-dose. In this manner, whole-body doses of either 150 or 200 r (table 1) were administered during a single session of about 20 or 25 minutes respectively.

Results

As its most striking feature, the initial reaction displays wide variability among persons exposed to similar, or even identical, doses. The present series corroborated previous findings,[3] symptoms in patients ranging from complete absence to severe prostration. This dramatic individual difference of unknown origin, together with the difficulty of assessing complications possibly caused by the preradiation disease, renders the group of 11 patients much too small for derivation of a typical clinical picture. Yet, from a comparison of present findings with previous reports on early consequences of both therapeutic[3] and accidental[2b] whole-body exposure, the characteristic initial reaction emerges with reasonable accuracy.[6]

Typical Clinical Picture.—Throughout the time of exposure, radiation induces no sensations and the patient remains completely asymptomatic. After completion of treatment, this freedom from symptoms continues for about one or two hours–the "delay period."[8] Then, rather abruptly, the reaction starts with the onset of fatigue, listlessness, and apathy. Usual activities are discontinued; lying down on his bed, the patient withdraws more and more from his environment and appears depressed. Not infrequently, he describes his condition as "washed-out" or "worn-out," and complains of dizziness, dulness, and headache. This "fatigue complex"[7] is accompanied as a rule by concurrently developing signs and symptoms pointing to the gastrointestinal tract. Loss of appetite and complaints about an "upset stomach" suddenly occur around two hours after exposure. Nausea, frequently associated with spells of frank vomiting, soon supervenes and increases in intensity until it reaches a climax somewhere between five and eight hours after irradiation. At that time, the combination of "fatigue complex" and "vomiting complex" may lead to pronounced weakness or even to prostration.

After passage through the climax, the reaction steadily recedes; intervals between bouts of vomiting lengthen, emeses decrease in number as well as in volume, until they disappear completely. Nausea, anorexia, and fatigue then subside in that order. Because of the gradual ebbing of the succession of exacerbations and remissions, the duration of the initial reaction cannot be defined accurately, but the usual course is as follows: On the second day, moderate nausea and occasional spells of vomiting still persist but the general condition is markedly improved; on the third day, the patient becomes asymptomatic.

Special Observations.–To fathom its potential impact on populations engulfed by nuclear disasters, the initial reaction demands special analysis from two aspects–length of delay time and extent of disability.[8] Length of delay time, obviously, is important because the interval between radiation exposure and the onset of clinical symptoms represents the period during which an exposed group remains in full possession of physical fitness and mental alertness–faculties so vitally necessary for well-organized active evacuation of disaster areas. The extent of disability, on the other hand, requires careful consideration because of its significance when evacuation cannot be executed or completed within the delay time; the initial reaction, unfolding among members of the afflicted population, will impair capabilities for active participation in escape, rescue, and other emergency efforts. Again, for a reasonably accurate assessment of these two important factors, the present findings are insufficient and must be supplemented by previous studies.[9]

Civil Defense Considerations

The delay time is known most reliably for patients who experience reactions leading to vomiting. Owing to its occurrence shortly after onset of symptoms, the first emesis strikingly and dependably marks the beginning of the initial reaction and is thereby indicative of the length of the delay period. That this period has a characteristic duration is strongly suggested by comparing, in table 2, the following sets of evidence: first, the present findings; second, a part of the results of Miller and co-workers[3]–of 30 patients exposed to 200 r, observations are presented only for those who vomited during the first 24 hours after treatment; and third, data reported for the Y-12 accident.[9a] Most conspicuously, the table demonstrates three points: (*a*) when vomiting develops at all during the day of exposure, the initial emesis consistently occurs in the interval starting at one hour and ending at five hours after radiation; (*b*) in the several-hundred-roentgen range, length of the delay period is barely affected by dose; and (*c*) agreement between therapy and accident data suggests irrelevance of radiation type (roentgen, gamma, neutron, or any mixture of these penetrating rays).

TABLE 2.–*Delay Time Elapsing Between Start of Whole-Body Irradiation and Onset of Vomiting on Day of Exposure*[*]

	Cancer Patients					
	Present Series		Miller[3] Series		Healthy Persons	
Patient No.	First Emesis, Hr. After Treatment	Air Dose, r	First Emesis, Hr. After Treatment	Air Dose, r	First Emesis, Hr. After Exposure	Body Dose, rad
1	nausea only	150	2.0	200	2	365
2•	4.5	150	2.0	200	4	270
3	nausea only	150	2.0	200	asymptomatic	339
4	*asymptomatic*	150	3.0	200	2	327
5	3.3	150	3.0	200	nausea only	236
6	1.0	150	3.5	200		
7	3.5	150	4.5	200		
8	1.8	200	5.0	200		
9	1.5	200				
10	2.5	200				
11	asymptomatic	200				

[*] Observations on patients in the present series and that of Miller and co-workers[3] are compared with data from healthy persons involved in typical nuclear accident.[9]

The validity of the three points has been established by a comprehensive analysis covering additional therapy evidence and all known nuclear accidents.[6] Hence, it must be anticipated that a population exposed to radiation in the several-hundred-roentgen range will remain completely asymptomatic for one hour and will experience a negligible incidence of initial reactions during the ensuing hour. Consequently, for all practical purposes, the two-hour time limit represents the delay period applicable to a large group of persons, because, after transgression of this limit, the incidence of prodromal reactions rapidly reaches a maximum between the fourth and fifth hours after exposure. That, occasionally, vomiting may start on the second or even the third day has been reported for all groups–radiotherapy patients, persons involved in nuclear accidents, and Japanese bomb casualties; these rare, atypically timed manifestations probably can be explained as reactions to psychological stresses or to other complications.[6]

Disability.–Among members of the present series, there was extraordinary variation in disability, with respect to both extent and duration. Two patients remained completely asymptomatic and, obviously, retained full possession of capabilities existing prior to exposure. In two other patients, the reaction assumed the form of a mild indisposition characterized by fatigue, anorexia, and episodes of nausea, headache, and dizziness. Even during the period of definite discomfort, generally commencing about two hours and subsiding about eight hours after exposure, almost any degree of activity probably could have been performed if necessary.

Quite a different appraisal of the initial reaction, however, was necessary for the seven patients who developed vomiting. During the most intense phase, usually extending from the 2nd through the 10th hour after radiation, prodromal effects distinctly impaired their mental and physical capabilities. This impairment, caused by the combination of apathy and depressed mood with weakness and malaise, attained such a degree in four of the patients as to seriously hamper their execution of any task demanding more than well-drilled actions. In these instances, the clinical impression suggested that disability had progressed too far to be overcome, or decisively alleviated, by psychological factors–probably not even by the strong motivations inherent in disaster situations. Such a conclusion could be drawn beyond any doubt for one patient who, throughout 24 hours, experienced complete prostration and inability to walk. Thus, extent of disability among the 11 patients covered the entire scale from unnoticeable impairment to absolute physical incapacitation; when disability occurred, it prevailed mainly during the interval starting about 2 and terminating about 10 hours after exposure. How do these findings compare with previous data?

Comparison of the present series (G) with both the group studied by Miller and co-workers[3] (M) and the Y-12 patients[9] (Y) yields the following distribution of severity: completely asymptomatic–G 18%, M 21%, Y 20%; mild reaction not exceeding nausea–G 18%, M 18%, Y 20%; and marked reaction associated with vomiting–G 64%, M 61%, Y 60%. This close conformity between therapy and accident data is unexpected, because the Y-12 group received distinctly higher doses. An explanation probably must be sought in two factors: First, because of spontaneous tendency toward nausea, advanced cancer patients may react at lower doses somewhat more vehemently than healthy persons and, second, available data suggests that, within the several-hundred-roentgen range, severity of the initial reaction is not enhanced significantly as the dose exceeds the 300 r level.[6]

Despite similarity in distribution of severity, the patients in the present series and those of the Y-12 group apparently differed in degree of disability. In cancer patients, reactions accompanied by vomiting consistently induced such a marked reduction of physical and mental faculties as to seriously *compromise their performance of difficult or strenuous* tasks. In sharp contrast, of the three persons who vomited in the Y-12 group, two remained in relatively good general condition–even at the height of their reaction–although "mild weakness and over-all ill feeling" existed. Only one man experienced disability comparable to that seen in cancer patients–in this instance, however, disability probably resulted from a reaction that was psychogenic rather than truly physical.[10]

Obviously, caution must be exercised before definite conclusions can be drawn about the extent of disability incurred by healthy persons and by cancer patients, because the sets of data are too small and the significance for civil defense is too critical. Nevertheless, the following points require consideration: As mentioned above, patients with advanced cancer are likely to react somewhat more vehemently; furthermore, since the systemic disturbance represents an additional burden that must be borne by the organism already weakened from preradiation disease, a higher degree of disability is liable to ensue. Thus, with respect to civil defense applicability, observations on cancer patients are probably too pessimistic. Findings in the Y-12 group, on the other hand, are certainly too optimistic because these persons received medical care immediately after the accident and, shortly after onset of nausea, they received antiemetic medication with injections of prochlorperazine dimaleate.[9] It is difficult to decide whether marked disability failed to develop because of therapy or because, by chance, the persons involved possessed relatively low susceptibility. These possibilities must be considered seriously because other accident data closely agree with findings on cancer patients. The case reports of Hempelmann and co-workers[2b] contain several striking examples of the initial reaction which clearly demonstrate that some persons enter a phase of marked weakness or even of complete prostration; disability is most conspicuous during an interval extending from 2 through 10 hours after the accident.

The preceding analysis may be *summarized* briefly as follows: with regard to all aspects–distribution of severity, time course, and extent of disability–there is no difference between the initial reaction in cancer patients and that in healthy persons; however, induction of corresponding degrees of impairment requires lower doses for the first than for the second group.

Other Findings.—Other manifestations were surprisingly inconspicuous and equivocal among the cancer patients in the present series. At the height of the reaction—between the fifth and the eighth hour after exposure—five patients showed a slight elevation of temperature, a trivial acceleration in the rate of pulse and respiration, and a barely perceptible drop in blood pressure. Despite their failure to occur in the remaining six patients, these changes might represent true components of the initial reaction, because similar effects were observed in persons exposed to much higher doses during nuclear accidents.[26]

Report of Cases

To illustrate the points discussed thus far and to demonstrate the various types and degrees of clinical picture, the following three case histories were selected according to a stepwise increase in severity of the initial reaction. No significance should be attached to the fact that the preradiation disease involved abdominal structures in the two patients with the more pronounced forms of reaction, because similar clinical pictures were displayed by other susceptible patients who did not have such an involvement.

Case 3.—Throughout one year prior to admission a 61-year-old woman had suffered from recurrent pleural effusions of unknown origin, necessitating two thoracenteses. During the last few months of that period, she experienced a 25-lb (11.4-kg.) weight loss, shortness of breath with "fluttering" of heart, and enlargement of lymph nodes—particularly conspicuous in both supraclavicular and axillary regions. After admission, biopsy of a scalene lymph node revealed malignant lymphoma—Hodgkin's granuloma.

During the preexposure observation period, the patient was found to be in fair physical condition; throughout most of the daytime she walked about the ward and performed light work. Her morale was good; she liked to converse with patients, nurses, and physicians alike, and she displayed a positive attitude toward both her disease and her new environment. On Aug. 29, 1957, she had breakfast as usual about 8 a. m. Later that morning, total-body radiation (150 r) was administered as follows: first half-dose, 11:08 a. m. to 11:25; repositioning, 11:25 to 11:30, and second half-dose, 11:30 to 11:47 a. m. Completely unaffected by the radiation procedure, the patient resumed her usual activities soon after return to the ward; however, she expressed some resentment about the frequent close examinations. Her temperature, pulse, respiratory rate, and blood pressure showed normal values. At 12:30 p. m. she ate lunch with fair appetite. Around 1:30 p. m.—two and one-half hours after the start of exposure—a spell of malaise erupted suddenly; fatigue, headache, and anorexia appeared as the chief complaints, over which were superimposed brief episodes of nausea associated with regurgitations causing "sour" taste but no frank emesis. After one hour this wave of discomfort largely subsided and was followed by resumption of usual activities; however, listlessness and somewhat subdued behavior persisted. Although the 3:30 examination revealed a small rise in temperature associated with trivial fall of both blood pressure and pulse rate, the patient expressed no complaints. This practically asymptomatic state was interrupted by a second wave of apathy, anorexia, and nausea arising around 5:30—six and one-half hours after exposure. The period of discomfort lasted about two hours; thereafter, the patient returned to a completely asymptomatic state. During the following days, a few periods of poor appetite were the only complaints that conceivably might have been caused by the radiation treatment.

Comment.—The initial reaction of this patient stands out as two waves of mild indisposition, with no appreciable impairment of mental and physical capabilities.

Case 10.—Several months prior to hospitalization a 25-year-old man progressively experienced general weakness, exertional dyspnea, epigastric as well as substernal pain, and loss of body weight. On admission the most prominent findings were generalized adenopathy and a marked reduction of both capacity and distensibility of the stomach, which displayed large gastric rugae. Biopsy of the right lacrimal gland revealed infiltrations of small lymphocytes consistent with the diagnosis of lymphosarcoma.

During the preexposure observation period the patient complained of weakness, nasal congestion, and night sweats; however, he was able to walk and to participate in some activities. On Nov. 5, 1957, the patient had his usual breakfast around 8 a. m., and received total-body radiation (200 r) between 9:30 and 10 a. m. He then walked about the ward and conversed with other patients. This period of obviously unimpaired condition suddenly terminated at noon—two and one-half hours after the start of radiation—with the abrupt onset of marked anorexia and severe nausea, swiftly followed by a bout of vomiting. Lunch could not be eaten. Although vomiting failed to recur, anorexia and nausea persisted unabated until 4 p. m. and then gradually subsided. During the intense phase of discomfort—extending from two and one-half through six hours after exposure—the patient appeared apathetic, weak, and too listless to walk. At the height of the reaction his temperature rose to

100 F (37.8 C) while his pulse rate, respiratory rate, and blood pressure remained practically unchanged. Late in the afternoon, improvement became clearly evident; some supper was eaten at 5 p. m., and thereafter ambulation could be resumed, although slight listlessness still persisted. On the next morning the patient appeared asymptomatic and ate his entire breakfast with good appetite.

Comment.—The initial reaction of this patient caused a moderate impairment of mental and physical fitness which was clearly evident throughout a five-hour period starting at two and one-half hours after irradiation. During that interval, his ability to execute strenuous tasks would have been doubtful, at best.

CASE 5.—About three months prior to admission, a 69-year-old man noticed development of a tumor in the epigastrium. Growth of the mass was paralleled by increasing polydipsia, polyphagia, polyuria, and weight loss. Examination on admission revealed lymphadenopathy, particularly prominent in the left parietal and left axillary regions. Exploratory laparotomy and biopsy disclosed that the large abdominal mass was a malignant giant-follicle lymphoma.

During the preexposure observation period the patient's physical condition was fair; he liked to roam about the ward and to assist in little tasks. Displaying a bright and cheerful attitude, he easily and swiftly established friendly relations with other patients as well as with hospital personnel. On April 9, 1957, he had his usual breakfast around 8 a. m. Total-body radiation (150 r) was started at noon and was completed by 12:40 p. m. After return to the ward, the patient displayed his normal cheerful attitude in explaining to others the procedure through which he had just passed. Subsequent to the 1 p. m. lunch, eaten with perfect appetite, he slept for one hour, as was his custom. This completely asymptomatic period ended sharply at 3:20 p. m. when vomiting suddenly started. Concomitant with the onset of repeated emeses—producing large amounts of undigested food and watery fluid—increasing lethargy developed. Muscle strength, particularly in the lower extremities, was distinctly reduced, and the gait appeared unsteady and ataxic. The distress reached a climax between 5 and 6 p. m. At that time, the patient became prostrated and mentally depressed; his temperature rose from 98 to 101.2 F (36.7 to 38.5 C) while pulse, respiratory rate, and blood pressure remained unchanged; attempts at eating supper were answered immediately by such severe bouts of vomiting as to necessitate oral administration of 25 mg. of chlorpromazine hydrochloride. The period of intense disability lasted for about five hours. Around 8:30 p. m. marked improvement had already made its appearance, as indicated by resumption of ambulation, consumption of a small meal consisting of corn chips and oranges, and the drinking of some water. On the next morning, the patient appeared asymptomatic; muscle strength had completely returned, and breakfast was eaten with normal appetite. During the following days, no complaints related to the radiation treatment were expressed; however, some waves of anorexia, extending into the fourth postradiation day, perhaps must be regarded as the last remnants of the initial reaction.

Comment.—The initial reaction of the patient caused a severe transitory depression of both mental and physical capabilities; the period of disability began three and one-quarter hours after start of irradiation and lasted for about five hours. During that interval, diligent execution of any task would have been impossible.

Comment

The subsequent discussion of the initial reaction will center around two aspects—namely, first, its potential significance in the atomic age and, second, its therapeutic management.

Civil Defense Aspects.—When medical assistance is readily available, as it is in both radiotherapy and reactor accidents involving small numbers of persons, the initial reaction represents a bothersome but insignificant side-effect that, due to its short duration, rarely poses serious problems. This harmless disorder may assume quite a different role, however, when certain civil defense situations are analyzed.[8] Obviously, nuclear disasters can assume such dimensions that exposed persons, in order to reach medical facilities, may have to endure several hours of driving or walking through streets congested by vehicles and panic-stricken people. Thus, while on their way, they become affected by the disturbance and thereby suffer reduction of fitness at a time when ultimate physical and mental efforts are necessary for survival. In a small group of hypersensitive persons, reactions probably will attain such severity as to imperil escape from the disaster area without aid. Therefore, the disturbance must be taken into account by authorities designing evacuation plans and other emergency measures which require the active participation of exposed populations.

The several-hour delay between exposure and arrival at medical facilities also has another implication demanding the physician's attention: on admission, exposed persons may already display initial reactions. Radiation-induced dizziness, nausea, and vomiting—when occurring in patients with mechanical or thermal lesions, particularly of head and abdomen—can easily be mistaken for sequelae of these other injuries. Thus, unrecognized, the initial reaction may jeopardize proper diagnosis, prognosis, and classification of casualties.[8]

Therapy.—Owing to its unsolved pathogenesis, the reaction can be neither prevented nor treated with specific remedies. Nevertheless, clinical experience has firmly established several principles of management which, when properly applied, enable alleviation or even suppression of overt manifestations in many instances. Among these principles, psychological reassurance plays a leading role because, similar to motion sickness, the initial reaction frequently is aggravated by apprehension or introspection. Such reassurance becomes especially important in civil defense situations in which uncertainty and fear, triggered by the onset of nausea and vomiting, may grow so powerful as to induce an outbreak of mass hysteria in an uninformed exposed population. Education must center around two characteristic peculiarities of the initial reaction—namely, first, its brief transient course and, second, its relative insignificance as an indicator of received doses; in a wide dose range, the severity of clinical manifestations is determined much more by individual susceptibility than by the amount of radiation.[6] Radiotherapy experience demonstrates that proper psychological preparation frequently suffices for controlling the distress.

When these measures prove insufficient, however, additional steps must be taken. Among the drugs, probably all sedatives are beneficial; by contributing to the restoration of equanimity they support psychological measures, and by depressing the excitability of autonomic centers they raise the threshold for nausea and vomiting. Selection of type and dose of medicament is determined by the given situation; often, the drug of choice will be one that acts almost exclusively on the medullary autonomic centers but does not affect cortical functions. Since barbiturates possess certain deficiencies in this regard, they have been increasingly replaced by more effective chemicals developed during recent years—e. g., meclizine hydrochloride, prochlorperazine maleate, and chlorpromazine hydrochloride. According to clinical experience, the combination of psychological measures and drug medication leads to a satisfactory alleviation of the initial reaction in practically all cases. Only the occasional hypersensitive patient will develop disturbances of such a degree as to necessitate parenteral administration of fluid, glucose, and protein.

Summary

Early clinical manifestations displayed by 11 cancer patients after whole-body roentgen radiation in one single large dose are compared with previous reports of "radiation sickness" and with acute sequelae observed in persons exposed in nuclear accidents. From this comparison, the typical initial reaction to penetrating radiation in the several-hundred-roentgen range appears to be as follows: signs and symptoms—essentially in the form of fatigue, nausea, and vomiting—begin to develop within two to four hours after exposure; they reach a climax somewhere between five and eight hours afterward; and they completely subside on the second or third day. During the intense phase of the disturbance, extending from approximately 4 to 10 hours after exposure, about 60% of irradiated persons experience various degrees of disability.

Despite its transitory nature, the reaction may present a major medical problem in civil defense situations because of coincidence and, thereby, interference with evacuation plans and first-aid procedures. Therefore, the early sequelae of exposure to penetrating radiation require the attention of all physicians who may have to manage such emergencies.

Route 3, Box 512C (Dr. Gerstner).

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CLINICAL NOTES

NEW THYROIDECTOMY RETRACTOR

Lyman C. Blair, M.D., Houston, Texas

In performing total thyroidectomy or lobectomy for suspected carcinoma of the thyroid, it is necessary to retract the thyroid tissue. Current methods for doing this include the use of the Lahey goiter vulsellum forceps and the placement of silk or nylon sutures through the thyroid. The latter method seems to be the most common among the practitioners in my community at this time.

Both of these methods involve cutting and massaging (more bluntly, squeezing) of the thyroid tissue, while its circulation remains continuous with the general body circulation. Since both cutting and squeezing are involved, it would seem that there remains a possibility that cancer-cell emboli may be disseminated. At any rate, distant metastases may later become apparent, and the part played by the thyroidectomy in causing them may be impossible to assess.

I have devised a new type of retractor for thyroidectomy and removal of thyroid nodules, which I believe should save at least some wear and tear on surgeons' consciences (see fig. 1). Because of the slow growth of many thyroid cancers, with late metastases, it will require many years for assurance that dissemination can be prevented by the use of this retractor; hence, by the time it is really proved, it is hoped that systemically acting cancericidal drugs will have rendered it obsolete.

It consists of three hemispherical suction cups and appurtenances necessary to make them useful for the purpose intended. They are each about ⅝ in. in diameter and are arranged in a straight line; each is provided with a metal drain (or actuating) line, and these converge and join to a nipple. The nipple is to be attached to the suction apparatus available in all operating rooms, by means of the usual rubber hose. There is a finger ring or handle attached for application of traction after the device is in use. A metal strut helps maintain the cups in the proper position relative to each other.

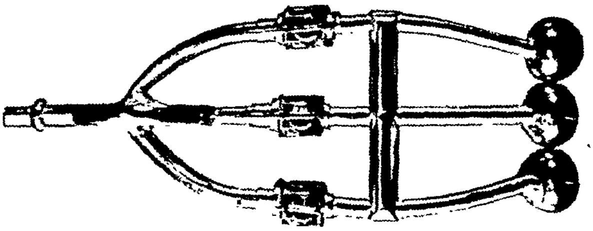

Fig. 1.—Chrome-plated brass retractor, with "three-way" valves.

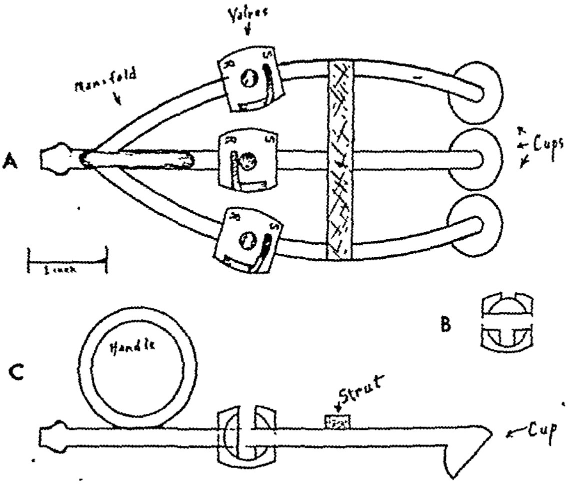

Fig. 2.—Suction thyroid retractor. A, plan view. B, valve in "suction" position. *C,* sagittal section, with valve in "release."

"Three-way" valves are placed in each individual cup's suction line (fig. 2). This is to provide for restoration of the pressure within the cup to atmospheric pressure, whenever it may become necessary to reposition these. If such valves were not used, the force necessary to release a cup from the tissue would be traumatic.

Due to the wide variations in the size and shape of thyroid glands, I deem it necessary to have at least three individual cups, with individual control. One, two, or three cups may thus be used at any given time, without the loss of effectiveness and the unnecessary noise which would result if one or more lines remained open to the atmosphere.

Although some compression of tissue will still result from the use of this device, there is no cutting; and, if the compression results in the freeing of cancer-cell emboli, there is a fair likelihood that they may be sucked into the retractor itself, where they will do no harm.

1212 Rothwell St. (2).

Member, Active Staff, General Practice Sections of Memorial, St. Joseph's, and St. Luke's hospitals.

COUNCIL ON DRUGS

Report to the Council

The Council has authorized publication of the following report.

H. D. Kautz, M.D., *Secretary.*

CURRENT STATUS OF THERAPY IN MICROBIAL FOOD POISONING

G. M. Dack, M.D., Chicago

Microbial food poisoning is frequently associated with acute illness of short duration. When the physician arrives in response to a telephone call, convalescence may be well under way. Because of the transient nature of the illnesses and the tendency for rapid convalescence, the general practitioner usually has had little opportunity to study them.

Microbial food poisoning falls into two principal categories. The first is one in which the causative microbes grow in a food and elaborate an exotoxin, for example, botulism and staphylococcus food poisoning. The second is one in which the causative living organisms multiply in a food product, and large numbers are required to produce infection. Examples of this group are Salmonella infections and food poisoning from certain streptococci, and from Bacillus cereus and Clostridium perfringens. Many of the viral and infectious agents may be disseminated in foods, but only those associated with gastrointestinal upsets are considered under the loose terminology "food poisoning."

In order for the physician to prescribe treatment, it is important that he have some idea as to the type of agent causing the illness. Implicated food may suggest the causative agent. However, before the implicated food has been determined, the symptoms, together with the period of their onset after a specific meal, are useful in directing attention to the causative agents. As an aid in finding the causative agent, the table gives the essential features of the various types of microbial food poisoning.

Botulism

Outbreaks of botulism are rare, and many types of illness have been confused with this disease, e. g., poisoning from pesticides such as sodium fluoride, methyl chloride poisoning, as well as cases of septic meningitis. In the United States the majority of outbreaks of botulism are related to the consumption of inadequately processed home-canned vegetables of low-acid content such as string beans, beets, and other vegetables. Usually there is evidence of spoilage by off-odors or flavors of such foods which are not a particularly good medium for the growth of Clostridium botulinum. Growth of the common types A and B of Cl. botulinum in meat products is accompanied by gross evidence of putrefaction, and for that reason such products are usually not eaten. In some homes, spoiled canned foods are given to chickens which develop limberneck and die. Such illness in poultry has sometimes provided the physician with useful clues leading to the diagnosis of botulism.

Five types of Cl. botulinum, labeled A, B, C, D, and E, are recognized. The types have certain biochemical reactions which differ, but their toxins cause the same kind of symptoms in man.

The mode of action of botulinum toxin in the body is not fully understood. However, the toxin appears to interfere with the production of acetylcholine, since a muscle in a physiological preparation poisoned by botulinum toxin will contract when acetylcholine is injected intra-arterially. A muscle in a similar preparation poisoned by curare does not react when treated with acetylcholine. Small amounts of either type A or type B toxin decrease the synthesis of acetylcholine in both in vivo and in vitro experiments. Some investigators have suggested an interaction of toxin, with the fine unmyelinated nerve fibers entering the end-plate region, thus causing a block of the nerve impulses. When the mechanism of the mode of action of botulinum toxin is discovered, perhaps a better treatment of the disease will be forthcoming. Until such a time, the only specific treatment is administration of antitoxin of the type causing the illness.

Each of the toxins is neutralized by a specific antitoxin. The most common types affecting man are A and B; type E less commonly, and types C and D have been rarely reported. Type E has been associated with fish or roe which has undergone spoilage. The treatment of botulism is, at best, unsatisfactory, and the mortality in the United States

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Director, Food Research Institute and Professor of Microbiology, University of Chicago.

is about 65%. If a physician finds patients with symptoms suggesting botulism, it is advisable to determine whether low-acid, home-canned foods have been consumed from one to three days previously. When symptoms are well advanced, antitoxin therapy is of little value. However, antitoxin will prevent damage by the toxin which is not already fixed in the central nervous system. At least 50,000 units of each of type A and B botulinum antitoxin should be given intramuscularly after the patient has been tested for hypersensitivity, and, if necessary, has been desensitized. At least 10,000 units diluted in 5 or 10% dextrose injection may be administered intravenously every 18 to 24 hours.

Enemas are recommended for washing out the colon to eliminate toxin which might be retained because of constipation. The physician should attempt to prevent aspiration pneumonia. Fluids taken orally are avoided in pharyngeal weakness or paralysis. The secretions in the mouth and throat should be aspirated continuously with a soft rubber tube and an aspirating machine. Fluid and electrolyte balance are maintained with dextrose and sodium chloride injection given intravenously. Oxygen is administered for cyanosis, and artificial respiration may be required. There is no agreement among clinicians regarding the value of respirators in the treatment of botulism.

In the treatment of shock, whole blood and plasma should be given. Antibiotics and sulfonamides should be administered in appropriate amounts to prevent secondary infections. The patient should be kept in quiet, restful surroundings and encouraged to avoid unnecessary muscular exertion.

Patients who have eaten generously of the incriminated food develop symptoms of botulism early, and antitoxin does not repair damage already done to the tissues. Frequently, persons who have eaten less of the incriminated food may be treated with antitoxin before symptoms appear, and there is an excellent opportunity for them to benefit prophylactically from the administration of antitoxin. Antitoxin should always be administered, since it will unite with uncombined toxin and prevent its damaging the tissues.

Staphylococcic Food Poisoning

Staphylococcic food poisoning is the most common type encountered in the United States. Since staphylococci are ubiquitous, it is impossible to protect foods from them. Enterotoxin-producing strains causing acne and other pyogenic infections may be imparted to food through handling. Many apparently normal food handlers may carry food poisoning strains in their nose and throat. Staphylococci can withstand high concentrations of sugar and salt, and for that reason certain foods may serve as a selective medium for them. In order for an outbreak to occur, a food poisoning strain of staphylococcus is required, a food in which it will grow, plus time and correct temperature. With a generous seeding of the right type of staphylococcus, five to seven hours at a warm temperature is sufficient for enterotoxin to develop. The site of action of enterotoxin in the body has not been established. Enterotoxin may be produced in vivo when the organism is confined to pyogenic lesions in the body or in the intestinal tract, where the normal intestinal flora is abolished by the action of large doses of broad-spectrum antibiotics.

Characteristics of Food Poisoning Caused by Bacteria or Their Products

Disease	Specific Agent	Intoxication	Infection	Symptoms	Onset of Symptoms after Eating	Foods Usually Involved
Botulism	Toxin of Clostridium botulinum	+	—	Difficulty in swallowing, double vision (diplopia), difficulty in speech (aphonia), difficulty in respiration, followed by death from paralysis of muscles of respiration	2 hr.-8 days; av., 1-2 days	Home-canned, low-acid products (toxin in food destroyed by boiling)
Staphylococcic food poisoning	Enterotoxin of staphylococci	+	—	Nausea, vomiting, diarrhea, acute prostration, abdominal cramps	1-6 hr.; av., 2½-3 hr.	Ham, cream-filled bakery goods, cheddar cheese, dry skim milk, poultry, potato salad (enterotoxin in food not destroyed by boiling)
Salmonella infection	About 600 serotypes of Salmonella, 40 of which are more common	—	+	Abdominal pain, diarrhea, chills, fever, frequent vomiting, prostration	7-72 hr.	Inadequately cooked egg products, poultry, or other foods
Streptococcic food poisoning	Enterococci	—	+	Nausea, sometimes vomiting, colicky pains, diarrhea	2-18 hr.; av., 8-12 hr.	Inadequately refrigerated foods contaminated with enterococci
Bacillus cereus food poisoning	Bacillus cereus	—	+			Starch foods inadequately refrigerated
Clostridium perfringens food poisoning	Clostridium perfringens	—	+			Poultry and meat products cooked and left unrefrigerated at warm temperature for several hours

The short incubation period after a specific meal is characteristic of staphylococcic food poisoning. Especially is this so when a number of people develop similar symptoms after a common meal. The severity of the symptoms depends on the potency of the enterotoxin in the food consumed. When small amounts of enterotoxin were fed to human volunteers, some developed vomiting without diarrhea and others cramps and diarrhea without vomiting. With the smaller amounts, the time of appearance of symptoms after ingestion of enterotoxin was longer, varying from four to six hours. When large amounts of enterotoxin were fed to human volunteers, the time of appearance of symptoms was shortened (45 minutes to 2 hours). Nausea, vomiting, cramps, and diarrhea occurred in the severe cases, and blood was found in the vomitus and stools. Acute prostration was usually present in severe cases, and patients might experience a sharp fall in blood pressure and develop shock. Death, although rare, may follow in debilitated persons or in very young children.

Perphenazine (Trilafon) has been found to prevent vomiting in experimental animals which are later fed enterotoxin. It has not been evaluated in the treatment of staphylococcic food poisoning in man.

Since the vomiting and diarrhea are pronounced in staphylococcic food poisoning, there is no need to administer emetic or purgative drugs. Vomiting and diarrhea are nature's effective method for eliminating unabsorbed enterotoxin. Abdominal pain may be relieved by codeine sulfate (30 to 60 mg.) or morphine sulfate (10 to 15 mg.). The most important therapeutic problem concerns dehydration and shock. Fluid balance should be restored by the intravenous administration of sodium chloride injection with 5% dextrose, 2,000 to 4,000 cc. in 24 hours. Patients adequately treated with fluids given parenterally recover quickly, and the period of convalescence is shortened. Caffeine sodium benzoate (500 mg. parenterally) may be required for severe prostration. Plasma and blood may be necessary therapeutic measures in the management of shock. Food or liquid by mouth is withheld until nausea and vomiting have stopped. Rice, clear broths, and tea may then be taken orally. Subsequently, the diet is enlarged gradually but limited temporarily to bland foods until the illness has subsided. Broad-spectrum antibiotics should not be given in the treatment of staphylococcic food poisoning, since many of the food poisoning strains of staphylococci are resistant to antibiotics. I am familiar with a patient who had a severe case of staphylococcic food poisoning and who was treated with large doses of chlortetracycline (Aureomycin) hydrochloride to which the causative staphylococcus was resistant. The patient developed a relapse of symptoms within 48 hours and died. Staphylococci ingested with incriminated food do not find conditions suitable for multiplication in the intestinal tract, since the normal microbial flora prevents their multiplication. Thus, it is important not to interfere with the normal microbial flora by the administration of broad-spectrum antibiotics.

Salmonella Infections

There are about 600 serotypes of Salmonella micro-organisms. Those concerned with the production of typhoid and paratyphoid fevers are not considered in this discussion. Approximately 40 types cause the majority of illnesses, which are food-borne and which give rise to infection lasting one or two days and commonly referred to as food poisoning. Some of these food poisoning strains invade the blood stream and cause infections lasting many days.

Salmonellae are abundant in nature and are found most commonly in the intestines of poultry and swine. They produce infection in animal species including cold blooded as well as warm blooded animals. They are present on the shell of eggs, and, when eggs are broken commercially, they find their way into frozen whole eggs, yolks, whites, and in dried egg products. These commercial egg products are used in the preparation of many food products including "convenience" foods, some of which are inadequately processed to destroy viable salmonellae.

Some students of enteric microbiology are under the impression that the incidence of salmonellosis is on the increase, as judged by the demand for serotyping of cultures; however, since there is no uniformity of reporting of these cases, there is no evidence to substantiate these impressions. Widespread outbreaks, due to specific unusual strains of Salmonella, have been reported which were thought to be related to food items in national distribution.

The predominant clinical picture is gastroenteritis, mostly mild in character, though a few cases may develop with typhoidal symptoms and fatalities among them. In one large outbreak in a city, there were 1,800 cases, with 11 fatalities due to Salmonella typhimurium. Complications are uncommon but include thrombosis, thrombophlebitis, pyelitis, osteomyelitis, dehydration and toxemia, arthritis, and, in young children, meningitis. Diarrhea may last for a few hours up to four to six days. Vomiting occurs occasionally.

The number of Salmonella organisms required to cause illness undoubtedly depends upon the age and susceptibility of the individual. Small numbers of organisms fed experimentally to some persons, although producing no illness, have sometimes resulted in a carrier state. From the public health standpoint it is desirable that no viable Salmonella, even in small numbers, be present in foods at the time they are eaten.

The treatment of Salmonella infections is largely symptomatic and is similar to that described for staphylococcic food poisoning. The intestinal tract is freed naturally of large numbers of Salmonella organisms by diarrhea, and only symptomatic treatment is needed.

Stool cultures should be made to determine whether Salmonella organisms are the cause of the illness. If symptoms of fever and toxemia are present for more than a day or if complications develop, a search should be made in the laboratory by sensitivity tests for an antibiotic to which the Salmonella strain is sensitive. No one antibiotic has been discovered to which all Salmonella strains are sensitive. In one large outbreak, oxytetracycline (Terramycin) hydrochloride, chlortetracycline hydrochloride and chloramphenicol (Chloromycetin) were used in treatment, with no appreciable benefit. In other instances Salmonella serotypes have responded to these and other antibiotics.

An antibiotic which is effective in vitro against a specific Salmonella strain should be administered to the patient in adequate dosage, with due precautions taken with reference to undesirable side-effects from the drug being administered.

Streptococcic Food Poisoning

Food poisoning caused by the alpha hemolytic streptococcus presents identical symptoms with that caused by B. cereus and Cl. perfringens, namely cramps and diarrhea, with only occasional vomiting, coming on usually 11 to 12 hours after eating a food item containing many millions of these organisms per gram. The incubation period may vary from 2 to 18 hours. There is usually no fever or leukocytosis, and the symptoms subside in the course of a few hours. No specific treatment is indicated, since the organisms do not establish themselves as a predominant flora in the intestinal tract. The mode of action of these agents in the production of illness has not been established.

When the streptococcus has been classified in several outbreaks, it has been found to be an enterococcus. This type of food poisoning has been studied in human volunteers, and, in many instances, illness has not resulted when large numbers of the enterococci have been fed. In other instances, illness has followed when freshly isolated cultures have been fed. More work is necessary to elucidate the mechanism by which illness results. Outbreaks have been associated with meat items and turkey dressing which have stood at warm temperatures for a number of hours, allowing profuse growth of enterococci.

Bacillus Cereus Food Poisoning

Outbreaks of food poisoning caused by B. cereus have been described in Norway. One large outbreak was traced to a ready-mix, vanilla pudding purchased from a grocery store, which was cooked and allowed to stand at a warm temperature until the following day when it was served. B. cereus is a spore-forming organism commonly found in the soil and therefore a natural contaminant of cereal products. The spores may not be destroyed in cooking and hence may germinate and grow rapidly in a food if conditions of moisture, time, and temperature are right. Illnesses have been produced in volunteers, but again more information is needed to determine the mechanism causing B. cereus food poisoning. No specific treatment is indicated since the symptoms are mild and of short duration. The diarrhea removes the organisms from the intestinal tract, and B. cereus fails to establish itself in the intestine.

Clostridium Perfringens Food Poisoning

Cl. perfringens has been found to cause many outbreaks of food poisoning in Great Britain. There is no doubt that many outbreaks occur in the United States, but seldom do laboratories examining implicated foods search for Cl. perfringens. The strains found to cause food poisoning produce extremely heat-resistant spores. Subcultures of strains from foods do not yield spores with the heat resistance of the original contaminants. The natural habitat of these strains is the intestinal tract of animals. Illnesses have been produced experimentally in human volunteers, particularly when the strain has been grown in a food which was involved in the outbreak. Negative tests among humans have occurred when old strains from outbreaks have been grown in common culture medium. The mechanism of the illness caused by Cl. perfringens is not understood. Outbreaks have commonly followed eating of meat products which have been cooked and allowed to stand at warm temperatures. In such instances the spores of Cl. perfringens contaminating the meat have not been destroyed but germinate and grow when the product is not refrigerated. No treatment is indicated for food poisoning from Cl. perfringens, since the symptoms are mild and the organism does not predominate in the intestine after the acute illness.

EYE-SIGNS IN HYPOTHYROIDISM.—Among the many signs of hypothyroidism, puffiness of the eye-lids is a familiar feature of the facial appearance, but watering of the eyes is not usually reported as a prominent symptom. Recently we have seen five patients who presented to an oculist complaining of watering of the eyes in whom there was found evidence of hypothyroidism and whose symptoms were relieved by the administration of thyroid extract. In two other cases which presented to physicians, one of primary hypothyroidism and the other of hypopituitarism, watering of the eyes and puffiness of the lids were prominent symptoms which responded to treatment with thyroid extract.—W. H. Smith, K. G. Howsam, and J. J. Billings, Epiphora, *British Journal of Ophthalmology,* October, 1959.

MEDICINE AT WORK

- *The Drinking Driver*
- *Teens in the Hospital*
- *The A. M. A. in Washington*
- *Words Across the Seas*
- *Federal Physicians*
- *Hobbies in Ohio*
- *Physicians' Radio*

Supererogation

A popular dictionary defines supererogate as "to do more than is required by duty or obligation," and at least one physician thinks it might make an excellent rule for doctors, when listening to patients.

Writing in the November issue of the *Medical Annals of the District of Columbia*, Dr. I. P. Frohman says, "The greatest complaint of patients is 'My doctor doesn't take the time to listen to me.'" And Dr. Frohman should know. He is the author of two recent and popular articles in a lay magazine which have resulted in his receiving hundreds of letters from concerned patients. He writes:

"These people, who represent a cross section of the United States, feel frustrated and restrained. They want to unburden, to talk to their doctors, but time does not permit this . . .

"Do we have a scientific computer to take the place of patient-to-doctor, doctor-to-patient talking and listening? And would you buy one if we had? I believe as did Osler and other eminent physicians through the ages that there will never be a test, a machine, or a method to take the place of just sitting and listening to our patients.

"We speak glibly of getting an accurate history from the patient . . . yet when the patient digresses a bit, he is gently, and sometimes not so gently, put back on the original trend of thought . . .

"Here then is the place for supererogation for the physician. Perhaps a small sign facing us squarely in the eye—LISTEN, DOCTOR—might be the solution for us and our patients."

Medics for the Multitude

Doctors Volunteer for Olympic Duty As Squaw Valley's Population Booms

Although more than 1,000 athletes are currently performing on acres of ice and snow at the VIII Olympic Winter Games in Squaw Valley, Calif., chances are that the spectators and not the participants will need the medical attention, and flu instead of fractures will lead the list of complaints.

Whatever the problems and wherever they are happening—on the slopes, rinks, jumps, or trails—Squaw Valley is ready for them, with all the manpower, facilities, and equipment likely to be needed. But there is no magic in this appearance of a topnotch medical service program. It took 14 months of planning by Dr. William B. Stiles, who is a professor of public health at the University of California at Berkeley when he isn't organizing Olympic health and medical services.

His preparations have been based on an estimated Valley population of 40,000 during the 10-day period of the games, but participants and other personnel began arriving Feb. 1, so it was then that the health and medical service really began operations. People are, of course, the key to Dr. Stiles's effort. He has 80 physicians on a billet list, and another 20 in reserve. There is also a pool of 60 nurses, although no more than 30 are expected to be needed at any one time. In addition, there are ambulance drivers, x-ray and laboratory technicians, physiotherapists, and even a dentist. Five persons—the chief physician, the assistant medical director, the chief nurse, a laboratory technician, and an x-ray technician—will be on 24-hour call.

All these people are working without pay, but they are being furnished with board and room. All are volunteers, although no

Skis swish through powder snow and skates carve the glittering ice, as thousands congregate for the VIII Olympic Winter Games. For the story of medicine's part in this sports spectacle, see the story above.

public plea was made. Somehow, the word got around, and the takers outnumbered the offers. Most of the volunteers are Californians, although some doctors from other states will take part. Special legislation will allow the out-of-staters to practice during the Olympic period. Both Nevada and California medical associations have approved the project.

Most spectacular of the services now in operation is the 10-man squad of skiing physicians. Spotted throughout the area, the doctors are instantly available for aid to disabled skiers and can be summoned either by radio or an emergency phone network.

The alacrity with which professional help volunteered leads Dr. Stiles to think that "They are all looking forward to their duties with the idea they'll get some fun out of it, but they know they're in for some hard work too." Duty periods have been scheduled to allow each volunteer some free time.

Mainstay of the facilities provided for the Squaw Valley medical service is a 28-bed, licensed hospital complete with an operating room capable of handling major surgery, although most patients needing surgical care will probably be evacuated to the nearby Tahoe Forest or Reno hospitals. Two Quonset-hut wards are connected to the main building by covered walkways. Food service is provided from a nearby kitchen. There are nine medical aid stations spread throughout the area. In addition, there are three training or physiotherapy rooms, a fleet of ambulances, several station wagons and over-snow vehicles, and offices for health personnel.

Ski patrols with years of experience in caring for injured sportsmen have pretty well standardized rescue techniques. Squaw Valley patrols will use an aluminum shell-type sled to remove the patient to the nearest aid station or ambulance point. Arrangements have also been made with the Stead Air Force Base at Reno, Nev., to airlift patients to a hospital, if need be.

To be genuinely useful, facilities demand equipment, and that problem has been met ingeniously too. The Department of Defense has loaned many items, and others have been offered by private firms. Pharmaceutical supply houses are providing medical supplies, with the understanding that unused items may be returned.

A Shot in Time

Heeding warnings of the possible outbreak of Asian flu again this year, Dr. Stiles began an immunization program two months ago, in an attempt to keep respiratory problems from wreaking havoc with the Games.

The possibility of such an occurrence was strongly impressed on him a year ago when flu cases outnumbered all others in a pilot run held during the trials for the American and Canadian teams.

Realizing that some of the greatest problems at the Games might result from a breakdown of sanitation measures, Dr. Stiles has assigned the task of overseeing them to a four-man squad headed by a professional health officer. The four are keeping a constant check on the area's water, milk, food storage and preparation, vermin control, and sewage disposal.

Medical care is available in the Valley for all contestants, officials, employees, and volunteers. Emergency care for spectators is furnished, but spectators needing continuing treatment are being referred to outside physicians.

Although he is modest about it, Dr. Stiles has a background well suited to the task at hand. As a former regional director for the Federal Civil Defense Administration, he is used to planning the medical care of large numbers of persons. And in 1952, he directed the health and medical planning for another major event held in California—the Boy Scout Jamboree.

Welcome Those Teen-agers But Monitor Their Actions

Magazines and Sunday supplements have painted many a glowing picture of adolescent volunteers at work brightening the days of local hospital patients, but the American Hospital Association warned last month that such blessings require adequate restriction.

An AHA-approved publication, entitled "The Teenage Volunteer in the Hospital," notes that such a program should be considered "primarily as an educational procedure, and part of the hospital's total community education program." Such areas as the maternity floor, the operating and emergency rooms, and the medical records section should be off limits to such teen-agers, the booklet says.

The publication notes, "No teenager should be allowed to have prolonged or sustained patient contact or [to] fill direct requests from patients. Neither should they be assigned to hospital-directed patient service outside the confines of the institution nor to any task which involves the handling of money."

The publication suggests that, ideally, such teen-age helpers should be between 16 and 18 years of age but that the age may be lowered to 14, contingent on the duties to be assigned and the supervision available.

What do the children get in return for their labors? "An opportunity to learn the moral satisfaction of constructive service to a community institution . . . and a sense of community responsibility."

Chemical Tests versus The Drinking Driver

"I had only two beers. Naturally I acted a little upset when the police told me I was being arrested." The speaker, a neatly dressed, mild-mannered man, was making his first appearance in court on a charge of driving under the influence of intoxicants. Arresting officers testified his automobile weaved, his breath was alcoholic, and he staggered and was belligerent.

His case is similar to thousands which judges and juries must decide every year on the basis of conflicting testimony.

How to remove much of the uncertainty is discussed in detail in a newly published A. M. A. manual, "Chemical Tests for Intoxication." Fourteen authorities shared in the writing of the 103 pages, bringing under a single cover material previously available only if gleaned from varied sources. The publication was prepared by the A. M. A. Committee on Medicolegal Problems and 1,500 copies have been printed for distribution to physicians without charge and to other interested persons for one dollar (see Medicine at Work, THE JOURNAL, July 19, 1958).

Traffic accidents in this nation kill 40,000 persons every year and injure many more. Dr. Herman A. Heise of Milwaukee, Committee Chairman, cites four independent surveys which show that one-third of the accidents are caused by a driver or pedestrian under the influence of alcohol.

Dr. Heise says intoxication would appear to be one of the easiest diagnoses for a physician to make, yet it is one of the hardest to substantiate in court. How, he asks, can the doctor prove the accused was not suffering from a traumatic brain injury, diabetes, multiple sclerosis, or any of a hundred other ailments with symptoms resembling those of intoxication? A wide disparity between popular beliefs about alcohol and scientific observations is noted by other authors who urge that evidence based only on opinion be mistrusted.

The Arizona View

Standards for judging drinking by drivers vary widely throughout the United States. There is one which has been selected as a model by the A. M. A. and the National Safety Council. It is the definition of the Arizona Supreme Court:

"The expression 'under the influence of intoxicating liquor' covers not only all the well known and easily recognized conditions and degrees of intoxication but any abnormal mental and physical condition which is the result of indulging in any degree in intoxicating liquors, and which tends to deprive him of that clearness of intellect and control of himself which he would otherwise possess.

"If the ability of the driver of an automobile has been lessened in the slightest degree by the use of intoxicating liquors, then the driver is deemed to be under the influence of intoxicating liquor. The mere fact that the driver has taken a drink does not place him under the ban of the statute unless such drink has some influence upon him, lessening in some degree his ability to handle said automobile."

Chemical tests for intoxication have been in use over 50 years, and more than 200 analytic methods of testing for the presence of alcohol have been developed. The manual provides instructions on conducting some common tests through sampling blood, breath, or urine. The reader is cautioned, however, that rapid adoption of testing methods could lead to mistakes which upset prosecutions and impair public confidence in the tests themselves.

Ideally, the phrase "under the influence of intoxicants" would mean the same in all states, perhaps all nations. How far the ideal is from reality is shown by legal writers, who review legislation and court decisions in various states.

The man who claims to have consumed only two beers (but actually lost count) might be acquitted in California, where courts have held that the prosecution must prove alcohol has reduced the defendant's driving ability below that of the poorest driver on the road.

Tests May Be Misused

This same defendant in Arizona probably would be convicted. The Arizona State Supreme Court definition has been praised as a model for other states to follow by both the A. M. A. and the National Safety Council. It says, in substance, that a driver is guilty if alcohol has lessened his driving ability in the slightest degree, although merely taking a drink does not place him under the ban of the statute.

As early as 1939 the A. M. A. House of Delegates advocated a threefold division of blood tests of defendants: (1) Any driver whose blood showed a concentration of 0.15% of alcohol or more would be guilty. (2) Any driver whose blood test result showed 0.05% or less would be innocent. (3) A test result between these limits would be weighed along with other evidence in deciding guilt or innocence.

Some European countries have adopted the policy of convicting all drivers whose blood contains 0.05% or more. This could include some persons who actually had no more than two beers.

In the United States, on the other hand, judges and prosecutors frequently take the position that no person with less than 0.15% of alcohol in his blood should be prosecuted. One of the authors calls this "a perversion of the intent of the testing program," offering a refuge to many drivers who are arrested and actually are intoxicated.

The A. M. A. in the Capital

The Washington Team Serves Both Medicine and the Nation

The United States government now is spending about 4% of its budget on medical-health activities. In the current fiscal year the total is 3.16 billion dollars, not counting another 5 billion dollars paid to disabled persons under aid programs financed entirely or in part by federal funds.

What impact will expenditures of this size have on medical practice? What will be learned from research at the National Institutes of Health, for which 400 million dollars has been appropriated this year? Can private practitioners help the studies there? About 500 bills related to medicine were introduced in Congress last year. What is their status now and what new bills will be introduced this year? Administrative agencies almost daily are required to make decisions pertaining to health problems in the nation. Who will present the thinking of America's doctors?

A physician in Maine or California obviously is unable to keep abreast of affairs in government that are of interest to his profession. The A. M. A., however, tries to perform this service for him, through its officers, committee members and paid staff workers. A vital part of the work is performed by the Association's Washington team, which consists of 23 persons working out of an office at 1523 L St. N. W. The team includes physicians who maintain a liaison with the administrative agencies, attorneys who are familiar with the legislative processes, and journalists who report on Washington events of significance to physicians.

Dr. Roy T. Lester, manager of the Washington office, says it operates strictly as an extension of Association headquarters in Chicago. "We make no policy decisions. Our function is implementation of policy previously established by the A. M. A. policy-making body." Key men in Washington report directly to their division heads in Chicago. Daily contact between the two cities is maintained by teletype, and weekly group conferences are conducted by telephone to keep staff members in both cities fully informed.

Doctors Know Government

Dr. Lester, former medical director of Blue Cross and Blue Shield of Texas, is one of three physicians on the Washington staff, all of whom joined it last year. Dr. Otis L. Anderson, formerly with the U. S. Public Health Service for 30 years, retired as assistant surgeon general. Dr. Eugene V. Jobe was in the U. S. Navy for 30 years, retiring as director of the professional division of the Bureau of Medicine and Surgery.

Drs. Anderson and Jobe have both had lengthy assignments in Washington, giving them a familiarity with government administration which is useful in their present positions with the A. M. A. Division of Socioeconomic Activities. Inquiries related to medicine come from many sources. A West Coast physician is concerned over the medical care of migrant Mexican laborers. One of the physicians in Washington contacts the Labor Department on the matter. A midwestern congressman inquires whether a widely publicized drug offers any hope for a dying constituent. The lawmaker is informed of scientific findings on the drug. From a local medical society comes a report that a federal agency is infringing on private practice. Investigation shows that patients are being treated only as part of a research project.

James W. Foristel is one of three A. M. A. legislative representatives.

While Drs. Jobe and Anderson are concerned mainly with the administrative agencies, other members of the Washington staff follow congressional activities. Dr. Lester says the A. M. A. actually spends about one-third of its effort in the city in the legislative field, much less than many persons would suppose.

As many as 20,000 bills and resolutions may be introduced in a single session of Congress. They are analyzed by Washington staff member Paul R. M. Donelan, attorney in the A. M. A. Law Division, for any significant application to medicine. Proposed legislation in this category is channeled to the A. M. A. Council on Legislative Activities for study. The Council then recommends an A. M. A. position to the Board of Trustees. When congressional hearings are held and the Association is to submit statements or testimony, Washington office personnel assist witnesses who will speak for the A. M. A.

When the Association takes a stand on legislation, more often than not it is in favor of what is being proposed. The positive record of the A. M. A. was cited at its Annual Meeting a year ago to disprove charges that the organization has been basically negative in its attitude. In the 85th Congress, 15 bills of a medical nature were enacted into law and only one was opposed by the A. M. A.

Last year, in the first session of the 86th Congress, the Association submitted 22 statements to congressional committees. Only one was in opposition—on the Forand proposal to expand social security provisions to include hospital, nursing home, and surgical services for beneficiaries aged over 65. Twice representatives of the Association appeared before the Senate subcommittee on problems of the aged and aging to discuss medicine's activities in this field. On other occasions, the A. M. A. reiterated its support of the Hill-Burton program, endorsed a bill on automobile safety devices, supported regulations to protect consumers against hazardous household substances, and urged certain increases in research grants.

The Association has three legislative representatives who work with senators and representatives, their staffs, and the staffs of legislative committees that consider legislation of interest to the medical profession. The three, working through the A. M. A. Field Service Division, are James W. Foristel, Cecil B. Dickson, and Harold Slater. Mr. Foristel, with the A. M. A. since 1948, is a former practicing attorney, administrative assistant to a congressman, and general counsel of the House Small Business Committee. The other two men joined the A. M. A. staff last year and both have extensive experience as news reporters and editors.

Medical news from Washington often has one application for physicians and another for laymen.

Three physicians—Drs. Jobe, Lester, and Anderson—serve in the Washington office.

Ted Lewis checks Michelle Huggard as she teletypes Washington news to the Chicago headquarters.

Both needs are met by Ted Lewis and Dayton Moore, associate editors of the A. M. A. Communications Division. Through personal contacts and the teletype service of one of the major news agencies they keep abreast of day-by-day activities of committees and agencies. Columns are written by the editors for medical publications, including The Journal and the *AMA News* (published in Chicago and the successor to a newsletter formerly issued directly from Washington). The editors also handle relations with medical writers and reporters.

Widely varied activities are centered in the Washington branch—information is gathered from the special library maintained on medical legislation, mimeographed material is prepared for speeches and testimony, assistance is given visiting delegations from state medical societies. Yet the A. M. A. was in existence for nearly a century before it opened a permanent office in the nation's capital in 1944. The House of Delegates voted in 1950 to strengthen the office and a year ago it was reorganized for a closer coordination with Chicago.

Work of the Association often extends beyond national borders. Speaking before a Senate committee last year, Dr. Gunnar Gundersen, then A. M. A. President, said there is "a growing recognition that medicine, with its resources and influence fully mobilized, can perhaps do more for world peace than billions poured into armaments. There is a mounting conviction that the time has come when medical statesmanship must be used to augment the methods of political diplomacy."

The Federal Physician—His Future In the A. M. A.

Physicians in federal service now number about 17,500, five times the figure of a quarter century ago. What will be their future relationship to the rest of the medical profession?

In search of the answer, the American Medical Association's Committee on Medical Facilities spent Jan. 9 and 10 in Washington, D. C., where concentration of government doctors is especially high. For the past two years the Committee has been making a study to determine whether A. M. A. should revise its membership requirements to meet changing conditions in medical practice and American life generally. The study is concerned not only with federal service physicians but also with those in teaching, research, insurance, hospital work, and other types of nonprivate practice.

Dr. Willard A. Wright, Chairman of the Committee, promised that its report will be submitted to the Council on Medical Service in time to be ready for the House of Delegates in June.

Historically, most of the physicians in the United States have been in private practice and A. M. A. membership has centered on the local societies. Today, however, of all doctors active in medicine, one in every three is in nonprivate practice.

The number of active physicians rose from 150,419 in 1931 to 228,658 in 1959, while the percentage of those in private practice dropped from 86 to 68, according to surveys taken in those years. In the same period, the number of physicians in general practice or a part-time specialty dropped from 112,116 to 83,160. The number in a full-time specialty rose from 22,152 to 78,532. The number in nonprivate practice rose from 16,151 to 66,966, including those in federal employment.

Should a local medical society meet the needs of both the private practitioner and the government physician? To find the answer the Committee met with representatives of medical societies of the District of Columbia; Montgomery County, Maryland; and Arlington County and Alexandria, Va.

All Agree on Goal

Dr. Wright noted that in previous meetings the Committee had found that "Everyone agrees the A. M. A. should represent all doctors, whether they are in private practice or not." There was no objection to this ideal from the local society representatives. One of them observed, "We are all physicians; we are all working toward the same goal."

Representatives of the local societies, however, cited some practical difficulties in admitting any large portion of the federal doctors as members. They frequently stay in one community only a short time. They have little direct interest in some of the society's services to the locality in the areas of public forums, mental health, public health, and guidance. They may share an interest in scientific programs but not in the problems of private practice.

The Committee noted that lack of a license is the most frequent technical reason why a physician is disqualified from membership in a society. Other reasons may be inadequate period of residence in the community and the type of practice in which the physician is engaged.

A separate conference was held with medical officers of the U. S. Army, Navy, Air Force, Public Health Service, and Veterans Administration. Most physicians in these branches now hold a service membership in A. M. A., given to them free, without requirement of membership in a local society and without voting privileges. Would these doctors want to trade their present status in A. M. A. for regular dues-paying membership?

Keeping the present policy was favored by most of the medical officers who conferred with the Committee. They said the service membership often provides a pleasant introduction to organized medicine for the young doctor before he is permanently settled. The present arrangement also was said to allow for considerable professional and social contact between doctors in military service and local medical societies.

How is A. M. A. to serve all physicians equally well? The problem, predicted one Committee member, will be solved in time. "But the solution cannot be imposed from the top. It must come from the local society."

Dr. Willard A. Wright of Williston, N. D., is Chairman of the A. M. A. Committee on Medical Facilities. Other members are Drs. William F. Costello of Dover, N. J.; Charles L. Hudson of Cleveland; Robert L. Novy of Detroit; David H. Poer of Atlanta; John M. Rumsey of San Diego, Calif.; W. C. Stover of Boonville, Ind.; and Walter E. Vest of Huntington, W. Va. Dr. Edward C. Rosenow Jr. of Philadelphia is a Committee consultant and Mr. George W. Cooley of Chicago is staff secretary.

Doodlebug's Delight

Specialization, the medical motif of the 20th century, has extended even to parking lots.

One such transportation terminus, at the rear of the Multnomah County (Oregon) Hospital, has been set aside solely for the storage of compact foreign or American cars. According to Dr. Jarvis Gould, assistant administrator at the hospital, the experiment has been a success, and the capacity of the formerly 22-car lot has been raised by 4.

The hospital was backed by precedent, however. The University of Oregon Dental School once had a space devoted only to the parking of motor scooters.

Cooperation Marks Prison's Medical Care Plan

Why do many prison inmates readily volunteer for experiments in medical research? "The same reason you would," says Warden Douglas C. Rigg of Minnesota State Prison, at Bayport. "The only way medical science can advance is through public cooperation. Some persons donate money, some blood, some time, and some help in this way."

Two years ago Warden Rigg worked out a prison medical care program with the University of Minnesota Medical School and Mount Sinai Hospital in Minneapolis, a teaching hospital for university medical students. Research, although incidental to the program, has been conducted in various fields.

Warden Rigg estimates that 700 inmates have participated voluntarily in experiments. Since the prison population is about 1,300, the rate of participation is high, even considering the turnover and the fact some men volunteer more than once.

Before the medical care program was worked out, Warden Rigg says, the prison had difficulty in employing physicians. Now this need is filled by two medical residents—one in internal medicine and one in surgery—who are assigned to the institution for a six-month period and are on call at all times. They work under the supervision of physicians in the medical school.

The prison's program, which Warden Rigg says was started to meet the health needs of prisoners, has developed into a threefold benefit: Care for inmates, training of young doctors, and service to humanity.

Auxiliary Project Produces Better Baby Sitters

Parents in Seattle and King County, Washington, should have less difficulty these days finding a qualified baby sitter. More than 5,000 of the area's teenagers attended child-care classes last year.

Physicians, who often hear of emergencies caused by inexperienced child tenders, donated their time for the classes, held in junior and senior high schools. The course was started four years ago by the Seattle-King County Safety Council and the Women's Auxiliary to the King County Medical Society. In the present school year free time is being donated by seven doctors and one doctor's wife, Mrs. William Halliday, president of the Nurses' Alumni of the University of Washington.

Girls may use the information either in caring for someone else's children or in caring for their own, later in life. The program also helps the medical profession build better public relations.

The students are taught the dangers of sharp toys, small objects, poisons, and hot food. They learn how to change and bathe a baby safely and how to put him to bed. The instruction also stresses the responsibilities of parents in the selection of the sitter and the leaving of special instruction and emergency telephone numbers.

Similar programs have been conducted in many other cities, with use of kits supplied by the National Safety Council. The trainees are called Good Emergency Mother Substitutes, or GEMS, a gauge of the value of the qualified sitter.

Calling the Doctor—Via Short-Wave Radio

From an amateur's toy of the recent past, short-wave radio is today a communication medium of tremendous economic importance. From taxicabs to trash trucks, and from steelmakers to security officers, Americans are making increasingly greater use of the band of radio frequencies that compose the short-wave spectrum.

Physicians, too, have eyed such communications with interest, but in many cases they have been disappointed by services that failed to measure up to their promise. It was for this reason, two years ago, that the American Medical Association, on the advice of its Committee on Radio Communications, petitioned the Federal Communications Commission for 12 frequencies for exclusive use by a Physicians' Radio Service. Since then the American Hospital Association has also petitioned for five frequencies for hospital purposes.

If the A. M. A. petition is successful in having the requested frequencies set aside for the exclusive use of physicians, it will allow professionally established, two-way radio services for all physicians desiring to subscribe. It is expected that such services will be supplemented by standard telephone and radio paging systems, depending on the type of service desired.

Last November, the FCC issued a proposed list of frequency allocations which, if followed, will set aside a total of 17 frequencies for transmission

The Squawk Box

The number of usable short-wave radio frequencies is limited, and the demand is heavy. These facts make it necessary for radio users to share frequencies. Low transmitter power and geographical separation usually preclude interference.

There are times, however, when things go wrong, as they did one day when the office receiver of a suburban Chicago water company began issuing strange commands. The superintendent spent a puzzling afternoon until it became apparent that he was receiving signals from vehicles engaged in an oil company test run in Utah instead of reports from his own repair trucks. Unusual atmospheric conditions were blamed for the odd reception.

of "urgent messages essential to the medical duties of the licensee . . . or essential to the efficient rendition of hospital or ambulance service." The FCC requested that interested parties file comments by Feb. 1 on the proposed frequency allocation and that these comments offer advice to the commission on the matter of further subdividing the allocation to separate physician, hospital, and ambulance calls.

If the proposed frequency allocation is granted, such networks will have a secondary use in addition to their day-to-day function—they will make an effective emergency system for rallying and coordinating medical efforts to alleviate the effects of natural or military disaster.

Health and Hobbies—Natural Combination in Cleveland

Physicians—like ministers, insurance salesmen, and mothers of small boys—are often accused of not practicing those things that they preach. This is considered to be especially true of the harried modern doctor who supposedly prescribes a hobby for every patient, but who can never find the time for one himself.

Unless the physicians of Cleveland differ greatly from their colleagues, however, the theory has little foundation. For not only do Cleveland's physicians enjoy numerous hobbies, but they have also exposed them to public view in a show last fall at the Cleveland Health Museum. Sponsored jointly by the Museum and the Cleveland Academy of Medicine, the show offered no awards, nor did it stimulate any competition. Its chief objective was to demonstrate what even time-pressed people can do for relaxation.

Although many of the medical hobbyists stuck to the usual arts-and-crafts pattern, some added unusual modifications and others pioneered. One doctor displayed pen-and-ink drawings on mental disease, which had served as illustrations for his hand-printed book "A Psychiatrist's Anthology." Another submitted a hooked rug, and a third a rebuilt Rolls-Royce.

Dr. Bruno Gebhard, the museum's director, thinks the show was a success. He writes, "One of the chronic complaints in this age of atomic anxiety seems to be 'I would like to do something along this line, but I don't have time.' By putting on a physicians' Hobby Show—physicians being recognized by the public as being a little busier than the average person—the Hobby Show proved quite effective in counteracting this argument."

The *Cleveland Plain Dealer* agreed. It stated, "If hobbies help relieve the tensions of their exacting profession, wouldn't a hobby be a good thing for any man?"

Colleagues Everywhere—A New Life for Old Journals

Some people send CARE packages, others "adopt" foreign children, but in a small town in Western Pennsylvania, a semiretired otolaryngologist mails out letters by the score as his contribution to world betterment. But the letters don't go to foreign countries; instead they go to American physicians who have expressed an interest in a new plan called "Colleagues Everywhere."

Colleagues Everywhere is a program originated by Dr. Charles B. Daugherty of Jeannette, Pa., and is the essence of simplicity. He suggests that, instead of being sold as waste paper, medical journals be given a second life by being mailed to physicians in foreign countries. His logic is this:

Physicians in many parts of the world are without any great amount of current medical literature, and since English has largely replaced German as the medical language of the world, American doctors with their vast amounts of such literature are in a position to make a contribution to foreign medicine for the cost of re-mailing old journals.

To put his plan into effect, Dr. Daugherty needed two lists: one of foreign physicians to whom the material could be mailed and one of American doctors willing to take on the job of mailing. The Pennsylvania physician got a start on the first list when he discovered a woman who could furnish the names of a number of doctors in India. With this as a start, he then began writing to nearby physicians, asking that they volunteer to take part in the project. Requests went to members of his own hospital staff, the membership of the Western Pennsylvania ENT Society, and the rolls of his county medical society.

By this time, Dr. Daugherty began to worry about replenishing his supply of potential recipients, and it was then that he struck gold. A chance conversation put him on the trail of a college group interested in a similar but less scientific project. Learning of his need, the group offered to furnish him with the names of as many as 250,000 foreign physicians in 22 countries.

Thus armed, Dr. Daugherty is now seeking converts to his plan. The Westmoreland County Medical Society has agreed to sponsor the program and has offered the use of its office space. The women's auxiliary to the Medical Society of the State of Pennsylvania has become interested, and several state and county medical society publications have published explanations of the idea.

Cost of participation in the project is slight. A mailed request to Dr. Daugherty at 603 Clay Ave. in Jeannette will bring an interested physician the name of a foreign doctor. Then for amounts varying from 14¢ to 24¢, medical journals may be mailed under the rate for printed matter to overseas destinations.

In assessing the first nine months of his efforts, Dr. Daugherty says, "The response has been good but not overwhelming, so that up to now I have been happy to handle it from my own office. To date, I have 65 doctors mailing to 83 overseas colleagues."

One reason Dr. Daugherty urges widespread participation in CE is that he visualizes it as a deterrent to the spread of communism. He says, "Doctors in some of these situations are the only literate persons in their communities and have great influence. If we can get an individual doctor to say 'America is good,' the whole community will say 'America is good.'"

Conclave in Chicago To Promote Home Care

In years past, care at home was what the patient got when he could not or would not go to the hospital. Today, an expanded concept called Home Care is being offered as a partial answer to the need for economical care with a high rehabilitative potential for the chronically ill.

In hopes that this concept—if properly nurtured—will bloom more profusely in the future, five of the nation's major health groups will hold a three-day conference in Chicago next April to "develop methods for stimulating the growth and expansion of organized home care." Sponsors will include the American Hospital Association, the American Medical Association, the U. S. Public Health Service, and the Blue Shield and Blue Cross Commission.

Organized home care programs, while far from numerous, have attained a continuing popularity in recent years. Often they have come into being when a hospital decides to extend the range of its services past its own front doors. Other programs have been developed by such community agencies as health departments or visiting nurse associations. But whatever their sponsorship, they have a common aim—the care, in their own homes, of selected patients who do not require all the treatment facilities of a hospital but who, lacking alternatives, would have to be hospitalized.

Conference invitations have been sent to approximately 50 persons who will represent organizations covering the entire spectrum of health and medicine. They will be assigned to four workshop groups.

Foremost among the source materials available to the conferees will be a preliminary report of a survey of the nation's home care programs. The study will be an updating of a similar effort in 1956, which produced a detailed listing of facts and figures on 31 programs. The number of programs now in existence is still in doubt, but it might well be more than double the 1956 figure.

Civil Defense in Russia— What About CD in the U. S.?

"If you believe the reports, every one in Russia knows how to use a gas mask. . . . every child who passes the sixth grade has had a first aid course."

The scope of civil defense in the Soviet Union was described in these words to a group of midwestern medical society representatives in Chicago, Jan. 23. Dr. Paul A. Lindquist, deputy for operations of the Health Services of the Office of Civil and Defense Mobilization, showed a series of colored slides of Russian civil defense posters.

"All this has taken place since 1955," Dr. Lindquist said. The Russian government, he said, has given two civil defense courses for the entire population and is planning a third phase. "The course includes exposure to a lethal gas for 15 minutes."

The meeting was attended by representatives of state societies in Illinois, Indiana, Michigan, Missouri, and Wisconsin, all part of OCDM Region Six. The meeting is one in a series sponsored by the A. M. A. Committee on Disaster Care to encourage physicians and others in the medical field to help promote the concept of civil defense at the local level. All eight OCDM regions will have been covered when the final meeting is held in Washington, D. C., on April 23 and 24.

Two differing views on the best approach for stirring interest in civil defense were heard in Chicago. Dr. E. P. Ludwig of Wisconsin said the greatest public support for civil defense has arisen when protection against natural disasters is emphasized. "If you don't, people just lose interest," he said. Doctors from other states agreed that earthquakes, tornadoes, fires, and similar catastrophes create more interest in civil defense than do discussions about what would happen in the event of an atomic attack.

Emphasis on the wrath of Nature was called a mistake by Frank O. Starr, director of OCDM Region Four. Mr. Starr said that, while civil defense has a peacetime application, its basic purpose must remain the same: preparing the nation to withstand a wartime attack.

He urged physicians to help combat what he called three widespread fallacies hindering civil defense in the United States:

1. That the military will take over in case of attack. He said the military would help but would lack the capabilities for taking care of the entire nation.

2. That the Soviet Union will not use the hydrogen bomb because it is too horrible. He said past performances and recent statements by leaders of world communism prove it remains a serious threat.

3. That no one could survive hydrogen bomb warfare. He said the survival rate of a nation would depend largely on its civil defense preparations.

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FREEDOM OF CHOICE

AT ATLANTIC CITY in June, and again at Dallas in December, the American Medical Association's House of Delegates proclaimed and reaffirmed the belief that the "free choice of physician is the right of every individual" and that such freedom of choice, together with free competition among physicians, constitute prerequisites to "optimal medical care." In so doing the House of Delegates, by inference, took a position in favor of individual freedom of choice in general and expressed a preference for maintaining a social, political, and economic framework in our society conducive to the preservation of such freedom of choice.

All too frequently the term freedom has been misused or abused. Perhaps this is inevitable when the concept of freedom is capable of stirring up considerable emotion in the human breast; indeed, some men have died for it, and many others have proclaimed their willingness to do so. Less often, however, have men had the patience to devote attention to the less emotional and more mundane restrictions on freedom when these do not directly affect them. Certainly it behooves members of the medical profession to give attention to the broader meaning of the term "freedom of choice" and to its implications.

If freedom of choice were to relate merely to the number of courses of action open to a person, it would be more accurately described as power of choice. But freedom of choice represents something more fundamental than power; it represents the right of the individual person to be a free agent in his interhuman relationships, to make his own decisions, to be free from the arbitrary authority of others, and to be able to choose how he wishes to use his services or property rather than to be subject to coercion by others. Freedom of choice means that the person is able to choose his own course of action and his own pattern of living, subject to the requirement that he shall not act so as to violate the freedom of choice of others.

Freedom in this sense, it should be noted, is freedom of, not freedom from or freedom to; the preposition is of great importance, for the latter represent not different aspects of the same thing but entirely different conditions. This calls to mind the famous four freedoms enunciated by President Franklin D. Roosevelt during World War II—freedom of speech, of worship, from want, and from fear—later called "a noble pun" by the British economist, Joan Robinson. The two pairs of freedoms were, in fact, of entirely different character. Mr. Roosevelt meant security from want and fear, not freedom or liberty. Many philosophers, including Franklin and Jefferson, have pointed out that freedom and security are inconsistent human conditions. Indeed, make freedom of choice into freedom from choice and one comes close to a definition of slavery.

The struggle and debate of our time is intimately related to this difference between freedom of choice and from choice. Such a difference relates to the alternative methods of organizing human activity and is not simply a struggle between the United States and the Soviet Union or between the free world and the unfree world. Human activity can be organized so that the individual person has freedom of choice or so that he has little or no choice. The latter is the technique of the totalitarian state while the former is the mechanism of the market place with limited government and the separation of political powers.

A freedom-of-choice society in the economic sphere is a market society. Individual economic transactions are conducted through the voluntary cooperation of reasonably well-informed persons in such a way that both parties benefit from them. A free-choice society provides a mechanism for bringing about coordination with a minimum of coercion. Human activities, so far as possible, are conducted in the market, not in the political sphere. In this way coercion of individual persons to conform is minimized and freedom of individual choice is maximized. Each person can choose the color of tie he wants, the architecture of his house, and the cut of his clothes. He does not have to submit to what the majority wants; he may make his own choice and get it.

This is, of course, exactly the opposite from that organization of society where decisions which could be made by the market are made on a political yes or no basis. Even if these decisions are reached by the expedient of democratic majority rule (which may be transitory) rather than by dictatorial fiat, the political decisions are the results of group pressures instead of individual choices.

We live in a society still essentially free, one that gives to the individual person the right not only to choose his physician but to make other choices as well. Indeed, we have even permitted the individual person to choose to use his capital and his services to advocate the abolition of freedom of choice itself. Throughout the history of mankind this sort of society has not been the general rule but the exception. Perhaps this is inevitable. The totalitarian collectivist principle is simple and straightforward; it appeals to those who say, "Do something now." The necessity of restraint, group and individual, the recognition of ignorance and the imperfection of human knowledge, and the denial of a millennium and the aim of establishing conditions that make life not perfect but workable—all these attributes of a free-choice society constitute a highly sophisticated doctrine.

It is sobering to see the growing number of so-called leaders of political thought or politicians who advocate an ever-growing governmental assumption of responsibility for all sorts of complex economic and social problems—full-employment, care for the aged, care for the indigent, government health services, subsidized housing, and so on and on. Yet the moral ethic on which our civilization rests emphasizes individual responsibility. Can such a civilization survive? Perhaps, but only if it recognizes the difference between freedom of choice and freedom from choice.

LEPTOSPIROSIS IN HUMAN BEINGS

Leptospirosis in human beings is an acute, self-limited illness caused by infection due to pathogenic members of the genus Leptospira. The disease was once considered to be rare in the United States and was diagnosed almost exclusively in the presence of renal damage, hemorrhage, vascular collapse, and other distinctive features of spirochetal jaundice (Weil's disease). It is now known that leptospirosis is widespread in the United States and that most of the patients are neither icteric nor critically ill. Eight different serotypes have been identified with the disease in human beings, and several others are known to infect animals. But despite the increasing awareness of leptospirosis on the part of physicians, there is reason to believe that many cases go undetected each year.

In the literature devoted to leptospirosis there are to be found many descriptions of supposedly specific syndromes caused by different serotypes, but a critical review of published case reports lends little support to the view that the leptospiroses constitute a group of distinctive syndromes. Rather, it is impossible to make a species diagnosis on clinical grounds alone, and the disease should therefore be described as a whole and referred to as leptospirosis rather than one of the many special names, such as canicola fever, swamp fever, or swineherd's disease, which have become so popular.

Basically, leptospirosis is a diphasic illness, with manifestations attributable in the first stage to leptospiremia and in the second stage to the body's immune response to the infection. The onset is characteristically abrupt, and the first four to seven days are marked by high fever, chills, headache, myalgia, gastrointestinal complaints, and conjunctival suffusion. Leptospires can be isolated from both the blood and the cerebrospinal fluid during this phase, but there is no meningeal reaction to the presence of leptospires.

The first stage terminates with defervescence and symptomatic improvement, but 12 to 72 hours later there is recurrence of fever and development of meningitis. Fever is usually of brief duration, and meningitis may be either subclinical or overt. Because the spinal fluid becomes sterile shortly after the onset of meningitis, the meningeal reaction of this phase can best be explained as the expression of an antigen-antibody reaction. Hypersensitivity has also been suggested as the basis for the neurological lesions which sometimes develop after the first week. Uveitis and leptospiruria are also features of this stage, but their pathogenesis differs from that already mentioned. They result from the proliferation of leptospires in organs where the concentration of antibodies remains very low—the anterior chamber of the eye and the tubule of the kidney respectively.

The prognosis in anicteric leptospirosis is excellent, regardless of therapy, but an appreciable mortality continues to result from spirochetal jaundice. This syndrome should no longer be regarded as a synonym for Leptospira icterohaemorrhagiae infection since the distinctive features of spirochetal jaundice can result from infection by any highly virulent leptospire, regardless of serotype. The term is useful for descriptive purposes, however, and should be retained.

The epidemiology of leptospirosis is now well understood. Man, an incidental and nonessential link in the maintenance of leptospirosis in nature, acquires infection either directly from the infected urine or tissues of affected animals or indirectly through contact with contaminated soil or water. The most frequent source of infection is stagnant water which has been contaminated by the urine of either domestic or wild animals. The portals of entry into the body are abraded skin and the externally accessible mucous membranes.

There is no conclusive evidence that antibiotic therapy appreciably alters the course of leptospirosis, despite the effectiveness of several agents in experimental leptospirosis. It is generally agreed, however, that therapy must be instituted quite

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Edwards, G. A., and Domm, B. M.: Human Leptospirosis, Medicine, vol. 39, Feb., 1960.

early in the course of illness if there is to be any benefit. Greatest effectiveness in treatment has been claimed for therapy with the tetracyclines.

The laboratory techniques for the diagnosis of leptospirosis are dependable, but, unfortunately, they are cumbersome and expensive and few laboratories are equipped for them. Several simplified tests are being studied, and, should one or more of these prove to be reliable, serologic testing for leptospirosis should become a standard procedure in public health laboratories.

REQUIREMENTS FOR AN IDEAL THROMBOLYTIC AGENT

At present, thromboembolic diseases represent a major cause of morbidity and mortality. An important therapeutic advance in the management of these problems was achieved by the introduction of anticoagulants. However, their use is designed to restrict extension of an already existing thrombus or to diminish the incidence of new thrombi or emboli; they have little, if any, effect on the immediate consequences of an acute thromboembolic episode. For this reason, much attention is being given to the development of thrombolytic (clot-dissolving) agents which could effect the rapid resolution of thrombi or emboli acutely formed within the vascular tree. Restoration of the circulation through the affected vessel might then limit the damage caused by vascular obstruction, and dissolution of the clot would remove a source of further embolization.

This new approach seems entirely feasible since fibrin, the major insoluble constituent of the clot, is susceptible to enzymatic lysis, and agents capable of effecting such enzymatic lysis may be expected to be delivered to the site of the obstructing thrombus after their introduction into the general circulation. Thrombolytic therapy, then, is based on the principle that thrombi can be dissolved enzymatically if the circulating plasma is endowed with an increased clot-dissolving ability for a long enough period of time. Sound evidence to support this contention has been obtained from laboratory studies, animal experiments, and, most recently, from controlled observations in man.

The problem of developing agents for practical therapeutic use is not simple, since a number of basic considerations must be satisfied. Lack of their recognition often results in unnecessary trial and error, as illustrated by an article appearing in this issue of The Journal, pages 912-915. The following basic considerations are most pertinent to the development of a safe, practical, and effective form of thrombolytic therapy.

1. The thrombolytic agents should have specificity for effecting the dissolution of fibrin but have relatively little effect on other circulating constituents. Proteolytic enzymes which act indiscriminately on a wide variety of plasma proteins cannot be expected to produce thrombolysis without hazardous consequences in other parameters.

2. It must be demonstrated that the administration of the thrombolytic agent induces increased plasma clot-lysing activity of the requisite degree; simple and rapid laboratory procedures should be available for showing that this activity has been produced and sustained in the patient's circulation during treatment. Frequently, the former has not been achieved, and reliable laboratory tests required for this purpose are still of an undesirably complex nature.

3. Thrombolytic agents should be properly standardized, and a technique should be made available for estimating the dose required for any particular patient. Current standardization for these agents is still unsatisfactory, and relatively little attention has been given to the differing abilities of patients to inhibit these agents.

4. The thrombolytic agents should not produce such undesirable side-effects as chills, fever, and hypotension—reactions which plague most of the preparations under current investigation. Though it may be argued that a severe pyrogenic reaction is small payment for the rescue of a doomed limb, it is unlikely that adequate thrombolytic therapy can be sustained in the presence of such a reaction, and the success of other procedures may be jeopardized by the time lost. Furthermore, since patients treated with these agents often will be critically ill, for example, after a coronary or cerebral occlusion, a severe pyrogenic or hypotensive reaction may result in a fatality. Such reactions with biological preparations are usually attributable to pyrogenic contaminants, and appropriate purification could eliminate this hazard.

Thus, an ideal thrombolytic agent would be a specific for effecting clot dissolution, adequately standardized, and capable of being given to patients without significant hazard, and it should be possible to estimate and control the dosage on the basis of simple measurements made on the patient's blood. In this respect, the development of some thrombolytic agents is more advanced than others, but clinically effective thrombolytic therapy, readily applicable to patient care, still awaits practical solution of all the problems raised. None of these problems is insurmountable; indeed, partial answers exist for most, if not all, of them.

The clinical needs for effective thrombolytic agents are so great that crash programs have been considered for their development. It would seem wisest to concentrate support on those studies aimed at rapidly solving the existing fundamental problems, for, immediately on their solution, this new and exciting field of therapeutics will develop quickly and spontaneously at the clinical level.

THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

Is there anything really sacred about recent predictions that the United States must maintain a specific physician-population ratio or the health of the nation will be in jeopardy?

I hope not. To me such a figure is merely a projected ratio which is a combination of current birth rates and population factors compared to output of new physicians and existing doctor supply. Hidden in the projected ratio is the assumption that our present experience with all these factors will continue through the next decade or beyond. By using the latest figures on physicians and population and by using estimates of the population of the United States in the years ahead, the ratio makers have shown that there is an increasing need for a stepped-up output of physicians through the next few decades.

Let me hasten to emphasize that I concur that an increase in the physician population will be necessary. Indeed, the number of physicians has risen steadily for many years. As the future market for medical care increases, I believe that physician population will rise to meet this desirable market demand. Contrary to the vocal opinion of some, medicine is not attempting to regulate supply. The record will show that medicine has welcomed and encouraged the training of more physicians.

I feel that too much stress can be placed on physician-population ratios and on the need to maintain the same ratio through the years. Is there really any reason why the nation should be bound to a rigid ratio?

It is my belief that projected ratios rely too heavily on factors that are not easily predicted—future birth rates and developments in medical science. I think that a significant development in population behavior or in medical science might occur which would reduce or increase the demand for physicians substantially in 5, 10, or 20 years.

I am confident that the general level of physician productivity and efficiency will rise considerably even though medicine becomes more complex. For example, space research is certain to give medicine fantastic new procedures in diagnosis and in health maintenance. New drugs also will enhance the effectiveness of medical care and treatment. A third major factor will be the extent to which paramedical health personnel is used.

Medical care today is not supplied only by a physician and the services he renders. The paramedical group now contributes extensively as a medical team member to a patient's care. In the first half of the 20th century the number of physicians increased 60%; in the same period the number of personnel in health services rose at least 400%. It is probable that in the remainder of the century health personnel will make comparable gains.

Furthermore, despite the new trends in population—more aged and more young people who need more medical attention—I believe that persons in the United States may require less medical care as the years go by. The number of "well" persons will grow as the general level of education rises, as more persons become sufficiently interested in their health, and as they take advantage of preventive medicine.

Thus, a physician-population ratio may be somewhat interesting, but it is merely an empirical relation between the number of physicians and the number of people. It is nothing more.

Louis M. Orr, M.D.
Orlando, Fla.

COUNCIL ON MEDICAL SERVICE

The Committee on Maternal and Child Care of the Council has reviewed the following report and endorses such activity. The Committee commends these two committees for their work in Illinois and suggests that this approach to a specific major cause of maternal mortality and morbidity may well be considered in other states.

CLINICAL REVIEW OF BLOOD LOSS IN 13,025 DELIVERIES IN THE STATE OF ILLINOIS

Almost five years ago the Illinois Gynecological and Obstetrical Society, through its committee on obstetric hemorrhage, undertook a unique project in clinical research at the grass roots level. Generalist and obstetric specialist members of the society alike have made a concerted effort to learn more about the causes, management, and prevention of excessive obstetric blood loss.

TABLE 1.—*Four-Year Summary of Operations of Joint Committee on Hemorrhage*

Yr	Cases Reviewed, No.	Av. Blood Loss, Cc.
1955	1,879	214.0
1956	1,428	184.0
1957	3,232	184.0
1958	6,486	175.5
Total	13,025	189.7

Simultaneously, under its chairman, Dr. Frederick H. Falls, the Maternal Welfare Committee of Illinois State Medical Society enthusiastically participated in the undertaking through its hemorrhage committee. Valuable consultation in preventive medicine was fully given by the deputy director, Dr. Don Rawlings, of the Division of Preventive Medicine, and the obstetric consultant, Dr. John Rendok, of the Bureau of Maternal Health, Illinois Department of Public Health. They contributed immeasurably to our joint accomplishments and plans for long-range objectives.

Over the years 1954-1958, statistical information (tabulated below) was supplied by Illinois physicians volunteering in this study. These physicians represented geographical areas outside the city of Chicago. The tables presented in this report are summaries made by the committee after careful study of information supplied them by their colleagues practicing in small towns and metropolitan areas alike.

At each annual meeting of the Illinois Gynecological and Obstetrical Society, the membership received a current report of the committee's work as a part of the regular agenda. Interest and enthusiasm have mounted over the years, stimulating the committee to enlarge its scope in accumulation and interpretation of data.

Table 1 shows the number of cases submitted by years. The estimated or measured blood loss is tabulated. Physicians submitting the data arrived at their figures either by actually weighing all linen soiled in delivery and extrapolating the quantity or by measuring blood collected in the basin placed against the perineum and estimating the blood on linen and sponges used. Whatever error exists with this simple procedure is probably a fairly constant one.

TABLE 2.—*Form of Initial Work Sheet*

To be mailed to: Dr. John Doe ________________ Hospital
0000 Main St. ______ Month of ______ 1958
Middletown, Ill.

Statistical Study for the Maternal Welfare Committee
Illinois Obstetrical and Gynecological Society

Patient, No.	Estimated Measured Blood Loss, Cc.	Gravida	Spontaneous or Induced Labor?	Type of Delivery	3rd day Hemoglobin Level	Was Cervix Examined or Visualized Before Removal from Delivery Room?

A statistical work-sheet was adopted for survey in 1958 (table 2). Table 3 is a completed summary of the 6,486 cases studied in 1958. Note the increased number of items tabulated.

Encouraged and inspired, the committee believed it should attempt to learn more about what happened to the babies in these cases. Thus table 4, the form sheet adopted for 1959, indicates our initial step in a clinical approach to neonatal deaths and allied casualties. With provision for three additional items of information, it is possible that our study may assume greater status as a pattern for obtaining data.

Conducted by Hemorrhage Committee, Illinois Gynecological and Obstetrical Society, and Hemorrhage Committee of Maternal Welfare Committee, Illinois State Medical Society. Members of these two committees who have contributed to this work are Drs. Willard C. Scrivner, Chairman; V. B. Adams; Ray Bucher; Carl Greenstein; A. B. Owen; Ralph Redmond; A. E. Ahlm; Hubert Allen; E. C. Bucher; A. R. Esposito; J. M. Kowalski; Howard Penning; and Worling Young.

Summary and Conclusions

This study in clinical work has been completely voluntary by all participants. There is, no doubt, error in method of estimation and measurement of blood loss but, we hasten to add, these are probably constant errors and do not affect trends indicated by the study. As a result of this and other efforts, we believe hospital obstetric personnel are more alert in anticipation, prevention, and treatment of excessive obstetric blood loss. As an added reminder, there is displayed in a conspicuous location in the delivery room of each Illinois hospital an enlarged plaque in red, white, and black, entitled "Dial for Safer Hospital Obstetrics."

TABLE 3.—*Summary of Cases Studied*

		Types of Blood Loss, Cc							
Deliveries, No.	3rd day Hemoglobin Level, Gm. %	Average	Greatest	Smallest	Average for Patients with Spontaneous Labor	Average for Patients with Induced Labor	Average for Patients with Spontaneous Delivery	Average for Patients with Operative Delivery Inspected, %	Cervix Examined or
54	11.5	151.0	500	100	150.0	170.0	...	...	..
83	67.7*	112.0	900	50	112.0	100.0	...	...	100.0
180	12.0	201.0	15,000	15	213.0	162.0	184 0	271 0	87.0
1,000	...	191.0	1,400	25	189.0	211.0	...	. .	57.0
194	...	168.0	...	...	...	...	..	...	...
93	11.0	229.0	1,325	15	210.0	350.0	..	..	61.0
280	13.6	201.0	2,000	20	198.0	217.0	...	...	64.0
415	11.6	143.0	700	30	144.0	117.0	154.0	159.0	17.8
836	12.0	191.0	1,500	5	189.0	209.0	171.0	260.0	...
301	80*	157.0	1,200	50	157.0	200.0	151 0	194.0	99.0
90	12.3	180.0	550	25	180.0	175 0	167.0	259.0	96.0
1,024	11.56	195.0	1,000	10	188.0	245.0	190.0	226.0	...
429	11.93	201.0	2,000	25	171.0	221.0	166.0	278.0	...
1,115	12.9	135.7	1,000	50	...	...	...	...	...
274	10.9	176.4	700	5	176.0	171.0	172.0	250.0	59.0
118	11.45	171.2	700	10	157.0	158.0	142.5	275.0	69.0
Total, 1958									
6,486	11.92	175.5	2,000	5	173.8	195.6	144.7	241.3	25.8
Grand Total 4 yr.									
18,025		189.7	2,500	5	175.9	190.2	156.3	243.1	...

* These quantities were reported as percentages of normal (normal for women, 12-16 Gm.%).

Objectives for the future are as follows: 1. To secure additional significant information along the lines we have conducted our past studies. 2. To evaluate and use data furnished by our colleagues for constructive purposes. 3. To emphasize anticipation, prevention, and definitive management of excess obstetric blood loss. 4. To make available the fruits of our endeavors to the education of medical personnel and those in associated disciplines. 5. To assist in successful education of the public to their responsibility in maternal and child welfare. 6. To develop acceptable and practical avenues of pursuit to assess ourselves in the prevention of infant deaths and associated casualties. 7. To develop closer relationships with fellow physicians in other states who have conducted or who wish to inaugurate a similar program.

TABLE 4.—*Revised Form of Work Sheet*

To be mailed to: Dr. John Doe
0000 Main St.
Middletown, Ill.

______________________ Hospital

Month of ______________________ 1959

Statistical Study for the Maternal Welfare Committee
Illinois Obstetrical and Gynecological Society

Patient, No.	Estimated or Measured Blood Loss	Gravida	Spontaneous (S) or Induced (I) Labor	Type of Delivery, Spontaneous or Operative	3rd Day Hemoglobin Level	Was Cervix Examined or Visualized Before Patient Left Delivery Room?	Baby's Birth Weight, Gm.	Baby's Fate—if Death Give Cause or Autopsy Diagnosis	Dismissed on What Postpartum day

ORGANIZATION SECTION

◆

A. M. A. GRANTS-IN-AID FOR RESEARCH

The Committee on Research of the A. M. A announces that the subcommittee on Grants-in-Aid is prepared to make grants up to $500 in 1960 to supplement clinical and basic medical science research. Grants will be made for the purchase of supplies, animals, and equipment but are not intended for the payment of salaries of full-time or part-time secretarial or technical help, labor, or overhead. No more than two awards will be made to any one institution. The tentative closing date for the receipt of applications has been set for April 1, 1960. More complete information concerning the program and application blanks may be obtained by writing to the Secretary, Committee on Research, American Medical Association, 535 N. Dearborn St., Chicago 10.

MEDICAL NEWS

COLORADO

Institute for Cancer Research.—Ground was broken recently for the two-million-dollar Eleanor Roosevelt Institute for Cancer Research at the American Medical Center, Denver. The dedication speech was given by Arthur S. Flemming, Secretary of Health, Education, and Welfare. Senator Richard L. Neuberger, Oregon, was also a speaker. The research unit will draw patients from the American Medical Center, a nonsectarian center founded in 1904 as the Jewish Consumptives' Relief Society. The center changed its name and began taking in cancer patients about five years ago. It is privately financed and offers free and unlimited care to patients for all stages of cancer. The research director of the institute will be Dr. Robert A. Huseby, of the University of Colorado School of Medicine.

ILLINOIS

Student Health Center.—Ground-breaking ceremonies for a new one-million-dollar student health center at Northwestern University were held Wednesday, Feb. 10, in Evanston. The new building, to be named the Searle Student Health Center, was made possible by an $800,000 gift from John G. Searle, vice-president of the university's board of trustees and president of G. D. Searle & Co., Chicago medical research and pharmaceutical manufacturing organization. The two-story health center will contain out-patient clinical facilities and general offices on the main floor and a 44-bed infirmary on the top floor. The level below the main floor will contain a small dining room, a nurse's lounge, a special laboratory, and classroom and storage space. The first floor will also contain a medical library which will house a collection of references concerning the health and psychological problems of young adults and will serve as a conference room for the health center staff. Completion of the building is scheduled for April, 1961.

Chicago

Nobel Prize Winner to Be Guest Speaker.—The British scientist, Sir Hans Krebs, will be special guest speaker at a symposium on ketosis to be held at Presbyterian–St. Luke's Hospital Wednesday, March 2. The symposium, which will include talks by specialists from across the country, is being held under the joint auspices of Presbyterian–St. Luke's Hospital and Ames Company, Inc., Elkhart, Ind. Sir Hans will present the first Dr. Joseph P. Ross Lecture, to be held at the Drake Hotel Wednesday evening. Title of his lecture will be "The Biochemical Lesion in Ketosis." Discoverer of the Krebs Cycle, Sir Hans is Whitely Professor of Biochemistry, Oxford University, and was Nobel Laureate in 1953. Other topics covered in the symposium will include the physiology of ketosis; ketosis in children; and clinical ketosis in adults. Members of the medical and related professions are invited.

Meeting on Medical Electronics.—Dr. William I. Freud, Skokie, will present "Spatial Vector Electrocardiography" at a meeting of the Professional Group of Medical Electronics, March 11, 8:15 p. m. Cocktails will be served at 5:30 in the lounge on the sixth floor of the Western Society of Engineers, 84 E. Randolph, Chicago. A speakers' dinner will be held at 6:15 p. m. The Professional Group of Medical Electronics is an affiliate group of the Institute of Radio Engineers, which was organized in 1912. The group is concerned with "the advancement of science and engineering leading to increased professional standing in its field and serves to aid in promoting close cooperation and exchange of technical information among its members." It provides a forum for discussion and presentation of papers for subjects of mutual interest. For registration at the March 11 meeting, call Mr. Charles F. Valach at COlumbus 1-2000.

Fund to Memorialize Dr. Carlson.—Efforts to establish an Anton J. Carlson Lectureship were announced by Dwight J. Ingle, Ph.D., chairman of the department of physiology, University of Chicago. Following the death of Dr. Carlson, Frank P. Hixon Distinguished Service Professor, and chairman of the department of physiology, faculty members expressed hope that some suitable means be found to commemorate his name. The suggestion most favorably received was the establishment, in perpetuity, of a distinguished lectureship bearing the name of Dr. Carlson. Dr. Ingle has undertaken the responsibility of raising the funds necessary to provide a "generous annual honorarium" so that the university can invite "the most eminent scientists" to speak on these occasions. Thus far, the appeal has been directed primarily to friends, colleagues, and former students of Dr. Carlson. Dr. Carlson's varied interests led him to make contributions in the areas of medicine, science, and industry; Dr. Ingle, therefore, is extending the appeal to individuals and groups who might welcome the opportunity to honor Dr. Carlson through the university he served.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Dr. Orr to Speak at Tuberculosis Luncheon.—Dr. Louis M. Orr, President of the American Medical Association, will be the principal speaker at the Tuberculosis in Industry luncheon March 17 at the Hotel Morrison. The luncheon will be held on the closing day of a two-day spring conference sponsored by the Tuberculosis Institute of Chicago and Cook County. Dr. Orr will be introduced by Dr. B. Dixon Holland, Secretary, Council on Industrial Health, A. M. A. The 10th annual conference, planned for doctors, nurses, leaders of industry, educators, and public health workers, will include a report of the last decade in the Chicago tuberculosis battle, an open forum on tuberculosis control, a symposium for patient approach to the tuberculosis alcoholic and his problems, and a report on advances in medical sciences. Dr. Morris Fishbein, medical editor, will speak on advances in medical science at the luncheon on the opening day. Prior to his speech, the Tuberculosis Institute Medal will be awarded. It is presented yearly to an individual selected for "his outstanding contribution to the fight against tuberculosis."

MARYLAND

Appoint Head for Physiology Department.—The board of regents of the University of Maryland approved the appointment of Dr. William D. Blake as professor of physiology and head of the department at the University of Maryland School of Medicine, Baltimore. Dr. Blake comes from Portland, Ore., where he was associate professor of physiology at the University of Oregon Medical School since August, 1952. Dr. Blake received his medical degree from Harvard Medical School, Boston, and served his internship at Presbyterian Hospital in New York City. He was a research fellow in 1948-1949 at the College of Physicians and Surgeons of Columbia University. In July, 1949, Dr. Blake went to Yale University School of Medicine, New Haven, Conn., where he was first instructor and later assistant professor of physiology.

MASSACHUSETTS

Dr. Lombard Cited.—Dr. Herbert L. Lombard, Boston, until his recent retirement director of the division of cancer and chronic diseases, Massachusetts Department of Public Health, was officially cited by the Commonwealth and the medical profession "for his contributions in the fight against cancer." Governor Foster Furcolo made the citation presentation Jan. 20 at the State House at a special ceremony. The citation was awarded "for distinguished service in the cancer field as administrator, research worker, and epidemiologist, for his inspiration to students and fellow workers, for developing and maintaining the highest standards in statistical work, for establishing data on cancer incidence, [and] for helping to make Massachusetts a leader in cancer control." Dr. Lombard won the top award of the Public Health Cancer Association of America in recognition of his "notable achievements" in 1953. He was director when Massachusetts became the first state in the country in 1926 to inaugurate a cancer control program.

University Grants.—Ninety research and training grants totaling $2,301,697 were awarded to the Harvard Medical School, the Harvard School of Public Health, and the Harvard School of Dental Medicine during October, November, and December, 1959, by the National Institutes of Health, Department of Health, Education, and Welfare, and by the National Science Foundation. The grants ranged in amounts from $2,500 to $121,499.

Alumni Hold Dinner Meeting.—The annual dinner meeting of the Tufts Medical Alumni Association will be held on Wednesday evening, March 30, at the Somerset Hotel, Boston. The guest speaker will be Senator Styles Bridges, who will present "Challenges of the Sixties." Dr. Christopher J. Duncan, Brookline, will preside. Dean Joseph Hayman will present "The Dean Looks at the Medical School." President Nils Wessel will also speak. The 25-year class, M'35, and the 50-year class, M'10, will celebrate their reunions at this time. For information, write Dr. Harry Blotner, Secretary, Tufts University School of Medicine, 136 Harrison Ave., Boston.

MICHIGAN

Dedicate Institute for Mental Health Research.—The University of Michigan Medical Center formally dedicated a $1,500,000 Mental Health Research Institute Building in ceremonies at Ann Arbor Jan. 29. Detlev W. Bronk, Ph.D., president, National Academy of Sciences, and Ralph W. Tyler, Ph.D., director of the Center for Advanced Study in the Behavioral Sciences, gave addresses at the dedication. The institute was established in temporary quarters four years ago. Its purpose, which will be accelerated in the new building, is a concerted attack on basic elements of mental illness, a health problem estimated to cost the American people an annual loss of 3 billion dollars and 325,000 man-years. Governor G. Mennen Williams spoke on behalf of the State of Michigan, and Dr. Jack Masur, assistant surgeon general, U. S. Public Health Service, represented the scientific interest of the federal government. State funds provided over three-quarters of a million dollars toward the construction of the research facility, with the balance coming from the U. S. Public Health Service. The McGregor Fund of Detroit contributed $100,000 for special equipment. The institute has a staff of over 60 scientists. The new building, located at the west end of the U-M Medical Center was opened for public inspecition Jan. 30. The structure has three floors of offices, conference rooms, workshops, and laboratories.

MISSOURI

Dr. Menkin Comes to Kansas City.—Dr. Valy Menkin, guest investigator at the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, was appointed professor of pathology and chairman of the department of pathology at the University of Kansas City School of Dentistry, Kansas City. Dr. Menkin started his appointment on Feb. 1.

MONTANA

Eye Bank Established.—The Eye Foundation, of Billings, was recently organized and will function primarily as an eye bank. It has received support from most of the service clubs in Billings, with the Altrusa Club the main supporter and founder. Named to the board of directors are Dr. Charles C. Morledge and Dr. James D. Morrison, of Billings. The Eye Foundation is the culmination of an interest of several Billings service clubs over the past three years and the eye bank will "fulfill a growing need for fresh corneas and stored vitreous in this community." Donor cards and information brochures will be made available to Billings physicians in the future. Information may be obtained by writing to the Eye Foundation of Billings, P. O. Box 703, Billings, Mont.

NEW HAMPSHIRE

Unit for Open Heart Surgery.—A program to provide care for children and adults suffering from diseases of the heart and circulatory systems has been established at the Mary Hitchcock Memorial Hospital, Hanover. This program includes the establishment of an open heart surgery unit and the expansion of research and diagnostic facilities. Dr. Richard H. Cardozo heads the open heart surgery unit. Recent purchase of a heart-lung machine by the hospital was made possible by a grant from the Spaulding–Potter Trust. Additional equipment was obtained through funds provided by an anonymous gift. Permanent members of the cardiac group, besides Dr. Cardozo, are Dr. Donald C. Andresen, director of the cardiac clinic; Dr. Mordecai D. Tyson and Dr. T. Richard Watson Jr., thoracic surgeons; and Dr. Roger E. Weismann, a surgeon specializing in diseases of blood vessels. Dr. Ferdinand J. A. Kreuzer, associate professor of physiology at Dartmouth Medical School, will be a consultant in cardiopulmonary physiology. The program conducted by the hospital will be closely related to the research activities of two affiliated organizations, the Dartmouth Medical School and the Hitchcock Foundation.

NEW YORK

Program for Treating Phenylketonuria.—New York State for the first time will go into the community to provide for children a treatment for the prevention of phenylketonuria, Dr. Paul H. Hoch, commissioner of mental hygiene, announced Jan. 29. The program is being organized on a research basis and will make it possible for physicians throughout the state to secure supplies of the necessary diet for patients if their financial circumstances are such that they require assistance. The diet will be supplied for all children up to the age of 5 suffering from the disease who are expected to respond to the treatment. An estimated 20 new cases of this form of mental deficiency occur each year in New York State, Commissioner Hoch revealed. The operation of the pilot program will be centered at Letchworth Village, Thiells, under the direction of Dr. George A. Jervis. All cases will be reviewed in the project center, Dr. Hoch said, but the general medical supervision of the patient will be in the hands of the family physician. Supporting laboratory services will be provided wherever requested. Information on the service may be obtained from Dr. Jervis at Letchworth Village, Thiells, N. Y.

New York City

Development Plan for Medical Center.—The Columbia–Presbyterian Medical Center announced Jan. 24 a development program requiring the subscription of 50 million dollars, the aim of the first joint appeal since 1928. Preparatory surveys for the program began nearly two years ago. An estimated 35 million dollars is sought for eight building projects. For endowment purposes 15 million dollars is desired to permit selective additions to teaching and clinical staffs and to support essential salary standards. General Lucius D. Clay, a trustee of Presbyterian Hospital, will lead the campaign. He has accepted the chairmanship of a newly created Columbia–Presbyterian Medical Center Develop-

View of a portion of the Columbia–Presbyterian Medical Center.

ment Committee of the two boards of trustees concerned. The development program combines three items in one major building project: an 18-story medical research building toward which William Black, president of the Chock Full O'Nuts Corporation and a Columbia alumnus, recently donated 5 million dollars; a library; and a structure to consolidate and house nonmedical services. These buildings will cost 21.5 million dollars. Seven further projects are a $3,200,000 residence hall for married students, residents, and research physicians; a $2,400,000 renovation of laboratories, classrooms, and lecture halls, and $1,100,000 auditorium; a $2,000,000 rebuilding of the second and fourth floors of Presbyterian Hospital; a $2,000,000 addition to transfer and increase doctors' offices; a $2,000,000 modernization of Babies Hospital; and an $800,000 estimate to centralize equipment for x-ray therapy within a single building. Sites for the new construction already are available within the 25-acre Medical Center.

NORTH CAROLINA

Clinic for Treating Cystic Fibrosis.—A new clinic for children and young people afflicted with cystic fibrosis was organized at the Duke University Medical Center, Durham. The new clinic is headed by Dr. Susan C. Dees, professor of pediatrics, and Dr. A. Douglas Rice, instructor of pediatrics. Working with them are other Duke pediatricians and members of the Medical Center's dietetics and physical therapy staffs. Cystic fibrosis patients have been treated on an individual basis at Duke for a number of years, Dr. Dees said. The new clinic "makes possible a better organization of time and hospital resources on their behalf." The Duke clinic will be held at 1 p. m. on the fourth Monday of each month in the Medical Center's pediatrics department. In addition to Duke pediatricians, a dietician will be on hand to give instruction about special diets, and a physical therapist will instruct patients in breathing and lung drainage exercises. The clinic resources are available to private patients and their physicians and to persons unable to bear the full cost of their medical care.

PENNSYLVANIA

Personal.—Appointment of Dr. Joseph R. Albrecht, Philadelphia, as full-time plant physician was announced by Alan Wood Steel Company, Conshohocken. Dr. Albrecht formerly was associate medical director of Reading Hospital and also had been director of professional services and associate medical director at Hahnemann Medical College and Hospital of Philadelphia.—Dr. Frank B. Metting was named as the Health Officer for the Allegheny County Health Department's Northwest District. He will provide full time medical direction for 31 municipalities and the North Side portion of Pittsburgh. For the past four and a half years, he has been in charge of the medical care and public health program for American Arabian Oil Company in the Dhahran area of Saudi Arabia.—John T. Cowles, Ph.D., professor of psychology at the School of Medicine, University of Pittsburgh, was appointed to serve a three-year term on the Selection Committee for the Senior Research Fellowship program of the National Institutes of Health, U. S. Public Health Service.

Philadelphia

Hospital Publishes Research Journal.—The Germantown Hospital of Philadelphia is having the first issue of its *Scientific Research Journal* published Feb. 15. It will be published periodically and will represent original research and other articles of interest. Hospitals wishing to exchange like publications are invited to write the Editor, Germantown Hospital, Philadelphia 44.

Temple Alumni to Fly to Paris.—Alumni of the Temple University School of Medicine will fly to Paris in two groups Feb. 29 and March 2 for a 10-day medical seminar and vacation trip. More than 120 alumni and their wives are signed for the journey, according to Dr. Robert M. Bucher, dean of the medical school. The alumni will spend two days visiting Paris hospitals and will be special guests at the American Hospital of Paris on March 7 for scientific sessions. Both Temple alumni and staff members of the host hospital will present medical papers. A farewell banquet on March 7 will be presided over by Dr. Henry C. Schneider, president of the Temple University Medical Alumni Association. This is the third consecutive year Temple medical alumni have held such special seminars. Previous trips were made to the Carribean and Puerto Rico.

GENERAL

Meeting of New England Allergists.—The New England Society of Allergy will hold its annual meeting and election of officers Wednesday, March 30, at the Longwood Towers, Boston. An afternoon scientific program will be held from 2 to 5 p. m. The annual business meeting will precede the evening scientific session at 7:45.

Conference on Physical Therapy.—The 37th annual conference of the American Physical Therapy Association will be held at the Penn-Sheraton Hotel, in Pittsburgh, June 26-July 2. The theme of the scientific program is "The Physical Therapist and Industry." The program will serve a two-fold purpose: (1) acquainting members with industrial medicine and (2) pointing up the potential role the profession should play in the field. Physicians, physical therapists, and scientists will participate. For information, write Miss Lucy Blair, 1790 Broadway, New York 19, Acting Executive Director.

Annual Fraternity Meeting.—The eighth annual interim scientific meeting of Phi Lambda Kappa, national medical fraternity, will be held at the Deuville Hotel, Miami Beach, Fla., March 20-27. The five-day program, starting Monday, March 21, will be for the benefit of the general practitioner and will feature papers and symposiums by specialists. Members of the medical and dental professions are welcome. For registration and information, write Dr. Samuel L. Lemel, 1621 Euclid Ave., Cleveland 15.

New Fifty Year Club.—Dr. John H. McCurry, of Cash, Ark., is interested in forming an A. M. A. Fifty Year Club in which membership would be limited to members of the Association who have been in practice 50 years or more. The first meeting of the new club is expected to be held during the annual clinical meeting of the Association in Washington, D. C., in November, 1960. Those who are qualified and desire to join this organization are requested to so advise Dr. McCurry, giving their complete name and address. Dr. McCurry plans to be in Miami at the June meeting to begin organizational procedures and to see any who qualify at this meeting.

Report on Deafness.—About 5,800,000 people in the United States have some degree of hearing loss, including nearly 110,000 who are totally deaf, it is reported by statisticians of the Metropolitan Life Insurance Company on the basis of current National Health Survey findings. Forty out of every 1,000 males have impaired hearing, a rate one-third higher than that for females. The higher rate among males is attributed to their more frequent involvement in accidents and their greater exposure to prolonged intense noise in industry. The relative frequency of hearing impairments rises rapidly with advance in age. From 8 per 1,000 persons under 25, the rate rises to nearly 130 per 1,000 at ages 65-74, and to about twice that figure at ages 75 and over.

Group Formed to Study Headache.—Recently a new society was formed, to be known as the American Association for the Study of Headache. The purpose of this organization is to bring together men who are interested in the study of headache and to allow them to discuss and express their viewpoints on current trends in this field. It is planned to have one formal meeting before the annual meeting of the American Medical Association. An informal meeting was held during the recent Southern Medical Association meeting in Atlanta. Officers include the following: president, Dr. Henry D. Ogden, New Orleans; vice-president, Dr. Walter C. Alvarez, Chicago; treasurer, Dr. Robert E. Ryan, St. Louis; secretary, Dr. Bayard T. Horton, Rochester, Minn.; Dr. M. Martin Tunis, moderator, Montreal, Quebec, Canada.

Society News.—Dr. Daniel C. Riordan, New Orleans, was installed as president of the American **Society for Surgery of the Hand.** Dr. George S. Phalen, Cleveland, was chosen president-elect. Dr. Phalen will take office in 1961. Other officers elected were: Dr. J. William Littler, New York City, vice-president; Dr. Don L. Eyler, Nashville, Tenn., secretary-treasurer; Dr. Robert M. McCormack, Rochester, N. Y., historian. Dr. Julian M. Bruner, Des Moines, the retiring president, was elected a member of the council.——Mr. Robert F. Butts, Birmingham, Ala., business manager of Southern **Medical Association,** was named executive secretary-treasurer of the 14,000 member association. He also retains his duties as business manager. Southern Medical maintains home office-headquarters at 2601 Highland Ave., Birmingham, Ala. Its 54th annual meeting will be held in St. Louis Oct. 31-Nov. 3.

Otorhinologic Meeting in Florida.—The American Otorhinologic Society for Plastic Surgery, Inc., will hold its convention and give a seminar in plastic surgery of the head and neck in Miami Beach, Fla., March 6-13 at the Deauville Hotel. Panels and round-table conferences will include the following subjects: blemishes, scars and keloids, fractures of the face; neck surgery; rhinoplasty; and otoplasty. *The program includes the following papers:*

Dermabrasion, Dr. Nathaniel B. Cole, New York City.
Principles in Treatment of Facial Fractures, Dr. Chester C. Woodburn Jr., Des Moines, Iowa.
Principles in Neck Surgery, Dr. Max L. Som, New York City.
Flexible Technics in Rhinoplasty, Dr. Morey L. Parkes, Los Angeles.
Flexible Technics in Otoplasty, Dr. Louis J. Feit, New York City.

The general business meeting and election of officers will be held at 2 p. m., March 7. Motion pictures of surgical plastic procedures will be shown March 8, 10, and 12. For information, write Dr. Joseph G. Gilbert, 75 Barberry Lane, Roslyn Heights, N. Y., Secretary-Treasurer.

International Nutrition Congress in Washington, D. C.—The fifth International Congress on Nutrition will be held in Washington, D. C., Sept. 1-7. An all-day symposium, "World Food Needs and Food Resources," Sept. 6 will be the main feature of the scientific program. The remainder of the program will consist of seven half-day sessions and panel discussions by invited participants, at which discussions are scheduled as follows:

Evaluation of Nutritional Status in Man.
Effects of Processing and Additives on the Nutritive Values of Foods.

Lipids in Health and Disease.
Animal Nutrition and Food Production.
Nutrition in Maternal and Infant Feeding.
Proteins and Amino Acids in Nutrition.
Three Hours Around the World—New Possibilities in Nutritional Research.

Special programs of 10-minute papers reporting unpublished original research will be presented concurrently with the panel discussions. Exhibits of laboratory instruments, books, foods, and other products will be on display. Visits to selected scientific laboratories are planned for Sept. 7. Simultaneous translations will be provided for the four official languages, English, Spanish, French, and German. For information, write the Secretariat, 9650 Wisconsin Ave., Washington 14, D. C.

Catastrophes in 1959.—Catastrophes—accidents in which five or more persons lost their lives—killed more than 1,400 persons in 1959 or about 150 fewer than in the preceding year, statisticians of the Metropolitan Life Insurance Company reported. In major catastrophes—accidents in which at least 25 people are killed—the loss of life dropped from nearly 430 in 1958 to about 175 last year, an "appreciably lower toll" than in any year since 1941. Four of the five major catastrophes in 1959 involved civil aviation. In February, a plane plunged into the East River in New York City, killing 65; another plane disintegrated in the air in a thunderstorm near Baltimore in May, taking 31 lives; in October a crash near Charlottesville, Va., killed 26; and 25 died when a plane rammed a mountain near Williamsport, Pa., on Dec. 1. The fifth major catastrophe was a series of earthquakes which took place on Aug. 17 in the area of West Yellowstone, Mont., claiming about 29 victims. Motor vehicle accidents were responsible for about two-fifths of the lives lost in all catastrophes last year. Fires and explosions accounted for about one-fourth and civil aviation for somewhat less than one-fifth of such deaths. The remaining fatalities were very largely due to natural catastrophes and to accidents involving military aviation, water transportation, and railroads.

Open Competition for Rehabilitation Award.—The R. D. Grant Company Award competition is open to all persons except members of the boards of governors of the American Congress of Physical Medicine and Rehabilitation, American Academy of Physical Medicine and Rehabilitation, and the program committee of the third International Congress of Physical Medicine. Manuscripts must be in the office of the American Congress of Physical Medicine and Rehabilitation, 30 N. Michigan Ave., Chicago 2, not later than May 2. This deadline will be rigidly maintained. The essay must not have been published previously and will be judged on original work, contribution to knowledge of this subject, and clear exposition of the facts. Contributions should not exceed 6,000 words, and the number of words should appear on the title page. Seven copies of the manuscript must be submitted—two original copies and five carbon copies. No papers will be returned. The winning contribution will be determined by the program committee of the third International Congress of Physical Medicine. All contributions will become the property of the American Congress of Physical Medicine and Rehabilitation and will be released to the *Archives of Physical Medicine and Rehabilitation* for publication. The winning essay will be presented at the meeting of the third international congress. The winner shall receive a cash award of $1,000.

Form Neuropathology Commission.—The Commission for Neuropathology was founded by invitation and in presence of the president of the World Federation of Neurology, Dr. Ludo van Bogaert, in the Salpertiere Hospital in Paris, Oct. 24. Neuropathologists from France, Denmark, Germany, the U. S. A., Norway, Switzerland, Great Britain, Poland, Austria, Sweden, Peru, and the Netherlands became constituting members. Prof. Dr. F. Seitelberger was elected secretary of the commission. Its permanent secretariat is: Institute of Neurology of the University of Vienna (Obersteiner Institut), Vienna 9, Schwarzspanierstrasse 17. The commission "claims independence for neuropathology as a proper medical discipline and emphazises the necessity of independent positions for full-time neuropathologists." It will examine neuropathology and neuropathologists in the different countries, will be interested in the preservation and care of the valuable neuropathological collections in different places. It will aim at giving all interested scientists use of these collections. One of the main tasks of the commission will lie in the "efficacious promoting" of scientific activities of neuropathology. Finally the commission is to be a consultative instrument within the World Federation of Neurology, e. g., for the advance of important projects of investigation. It was decided that an international journal of neuropathology, issued in several languages, would be published. For information, write Professor Seitelberger.

Award for Thesis on Laryngology or Rhinology.—The American Laryngological Association announced that, a sufficient fund having accrued from the Casselberry Fund encouraging advancement in the art and science of laryngology and rhinology, this sum is available in part or as a whole for a prize award. Theses must be in the hands of the secretary prior to Jan. 1 of any given year. The award is a prize of money with accompanying certificate signed by the officers of the association. It may be awarded in whole or in part among several contestants. Eligible contestants may be (1) hospital interns, residents, or graduate students in rhinology and laryngology; (2) an individual with an M.D. degree actively practicing or teaching rhinology and laryngology in the Americas; (3) any scientific worker in rhinology and laryngology. Manuscripts shall be presented to the secretary under nom de plume which shall in no way indicate the author's identity. There shall also be a sealed envelope bearing the nom de plume and containing a card showing the name and address of the contestant which the secretary shall keep. Manuscripts must be limited to 5,000 words and must be typewritten, double spaced on one side of the sheet. The thesis shall not have been published elsewhere. The successful thesis shall become the property of the American Laryngological Association but this provision shall not interfere with publication in the journal of the author's choice. Unsuccessful contributions will be returned. The award, made at the annual meeting of the association, shall be based on originality of material, scientific and clinical value, suitability, and method of presentation as to style, illustrations, and reference. The maximum amount of the award shall not exceed $200.

GENERAL

Warning on Mail Swindle.—Postmaster General Arthur E. Summerfield warned that the "Spanish swindle" mail confidence game, by which Americans have been cheated out of upwards of $100,000 a year, is again being actively promoted against the American public. The "Spanish swindle" mail racket operates as follows: basically, the intended victim receives a personal letter from a supposed banker or other respectable businessman in Mexico which usually reads: "A person who knows you and who has spoken very highly about you, has made me trust you a very delicate matter of which depends the entire future of my daughter as well as my very existence." The delicate matter turns out to be that the writer is in a Mexican jail for bankruptcy. He has, however, hidden away in a secret compartment of a trunk, some $450,000. The trunk is deposited, so the letter says, in a United States Custom House. To get out of jail and obtain the claim check for the trunk and pay other charges, will require $10,000 which the victim will be asked to bring with him to Mexico. In return for his trouble, the victim is promised a third of the alleged $450,000. If the victim is taken in he is told when and where to arrive with the $10,000 in cash. He is shortly relieved of this sum—often at the point of a gun—and is usually too embarrassed to report his loss. There is, moreover, no extradition treaty with Mexico covering mail fraud, and the Mexican courts have held that the victims are as guilty as the swindlers. In its more recent operations, lists were taken from "Who's Who in America" and other leading reference books.

LATIN AMERICA

Pan American Congress in Mexico City.—The next Pan American Medical Association congress will meet in Mexico City May 2 to 11, Dr. Joseph J. Eller, director general of the association, 745 Fifth Ave., New York City, announced. The scientific program, through its 48 different medical sections, will include all branches of medicine and surgery, dentistry, hospital administration, and medical education. New sections added since the last congress include space medicine, hematology, cancer cytology, and a section on general practice. Special panel discussions will incude pharmacology and new drugs, mental diseases, nutrition, relationship of dentisty to medicine, cancer research, sudden deaths, and medical press relations. The congress will also have scientific and commercial exhibits, medical motion pictures, and closed circuit television demonstrations of new techniques. Tours will be arranged to medical institutions by the Mexican Chapter of PAMA. The Pan American Medical Association was organized in New York City 34 years ago by a group of physicians for interchange of medical knowledge and research in the Western Hemisphere. They adopted as their credo: "The practice of medicine has no national, racial, or religious boundaries." For information on the congress, write Dr. Eller at the above address.

FOREIGN

Gerontology Institute in Switzerland.—The first international institute for experimental research into the comparatively new science of gerontology was established at the University of Basle, Switzerland, under the leadership of Prof. F. Verzar. Research work will be concentrated on the aging of the tissues of small animals which ordinarily have a short life span. The institute also will consider the aging of muscular tissues, the aging of nerve tissues, and the feeding of old people. The establishment of this international institute is the result of action begun some time ago in Basle when a research team of men and women specialists held a conference and started a study of gerontology. Other subjects under study include the harmful influence of fat accumulation and overfeeding on the life span, as well as problems concerning the toxic effects of products of metabolism.

Congress on Internal Medicine.—On Aug. 24-27 the sixth International Congress of Internal Medicine will be held in Basel, Switzerland, under the auspices of the International Society of Internal Medicine. Two main subjects form the principal program, "The Enzymic Regulation in the Clinic" and "Pathogenesy and Therapy in the Edema." The following are sub-topics:

Cardiovascular Enzymic Regulation.
Enzymic Regulation in the Liver.
Enzymic Regulation in Bones and Kidneys.

Cardiovascular Mechanism.
Tubular Functions.
Aldosteronism.

Panel discussions are planned on diuretics, nephrosis, and interstitial nephritis. Simultaneous translation for official languages will be provided. An exhibit of new research results is planned. Social functions include a special program for accompanying ladies. For information, write the Secretariat, Sixth International Congress of Internal Medicine, Steinentorstrasse 13, Basel, Switzerland.

Proctologists Meet in Rome.—The second symposium of Proctologica Latina, a society of proctologists of the Latin language, will be held May 13-14 at the Hotel Excelsior, Rome. The society organizes annual symposiums where foreign-language-speaking proctologists are presented as lecturers. For each meeting a panel is held headed by a moderator and four participants from different countries, and the subject varies every year. The program for the second symposium includes the following papers by invited participants:

The Surgical Management of Diverticulitis, Dr. Harry E. Bacon, Philadelphia.
Management of Polyps of the Rectum and Colon, Dr. Guy L. Kratzer, Allentown, Pa.
The Surgical Indications for Primary Resection of the Colon in Diverticular Diseases, Dr. James P. Fleming, Rochester, N. Y.
Treatment of Rectal Procedentia with the Délorme Operation, Drs. Richard M. Alexander, Jack W. McElwain, Sylvan D. Manheim, New York City.
The Clinical Importance of Melanosis Coli, Dr. Bruno Samenius, Goteborg, Sweden.
Poliposis Colonica—Treatment, Dr. Roberto A. Garriz, Buenos Aires, Argentina.

Proctologica Latina is legally established in Paris according to French law. For information, write Dr. G. B. E. Simonetti, Milano—Via s., Raffaele 3, Italy, Executive Secretary.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

American Board of Anesthesiology: *Written.* Various locations, June 24. Final date for filing application was January 10. *Oral.* Miami Beach, April 25-30. Applications already on file. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

American Board of Internal Medicine: *Oral.* San Francisco, March 30-April 1; New York City, Nov. 14-17. Closing date for filing application: Jan. 2 and July 1. *Written.* Oct. 17. Closing date for filing application is May 1. *Oral. Gastroenterology.* Philadelphia, March 11-12. Final date for filing application was January 15. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

American Board of Neurological Surgery: Examination given twice annually, in the spring and fall. St. Louis, April 10-12. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

American Board of Obstetrics and Gynecology: *Part II, Oral and Clinical.* Chicago, April 11-16. Final date for filing application was August 1. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

American Board of Ophthalmology: *Written.* Jan. 23, 1961. Deadline for filing applications is July 1. *Oral.* San Francisco, May 9-13; Chicago, Oct. 3-7. Sec., Dr. Merrill J. King, Box 236 Cape Cottage Branch, Portland, Maine.

American Board of Orthopaedic Surgery: *Part I,* Nashville, Denver and Philadelphia, Apr. 13-14. Deadline for receipt of applications was Nov. 30. *Oral and Written, Part II.* Miami Beach, Jan. 3-5, 1961. Final date for filing application is July 1. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

American Board of Otolaryngology: *Oral,* Chicago, Oct. 3-6. Final date for filing application is April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

American Board of Pathology: Memphis, April 21-23. Final date for filing application is March 7. *Examination in Forensic Pathology.* Memphis, April 22. Final date for filing application is March 7. Sec., Dr. Edward B. Smith, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

American Board of Pediatrics: *Written.* New York City, January 1961. Final date for filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

American Board of Physical Medicine and Rehabilitation: *Oral and Written.* New York, June 17-18. Sec., Dr. Earl C. Elkins, Mayo Clinic, Rochester, Minn.

American Board of Plastic Surgery: *Oral and Written.* Milwaukee, May 1960. Final date for filing application was January 1. Corresponding Secretary, Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

American Board of Proctology: *Oral and Written, Parts I and III,* Philadelphia, Sept. 24. Final date for filing application is June 30. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

American Board of Psychiatry and Neurology: San Francisco, March 14-15; New York, New York, Dec. 12-13. *Child Psychiatry.* Chicago, April 25-26. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

American Board of Radiology: *Examination.* Cincinnati, June 6-10; Dec. 5-9. Deadline for filing applications for the June examination was Jan. 1. Filing deadline for the December examination is July 1. A special examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

American Board of Surgery: *Oral Examinations (Part II):* New Orleans, Mar. 14-15; Kansas City, Kans., May 16-17, and Los Angeles, May 19-20. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

Board of Thoracic Surgery: *Oral.* May 1960. Final date for filing application was Dec. 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

American Board of Urology: *Written.* December. *Oral-Clinical.* Chicago, February 1961. Exec. Sec., Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 26.

DEATHS

Allee, Warren Logan Ⓜ Eldon, Mo.; St. Louis University School of Medicine, 1906; member of the House of Delegates of the American Medical Association from 1942 to 1952; past-president of the Missouri State Medical Association; member of the American Academy of General Practice; veteran of World War I; served as president of the Bank of Eldon; died in St. Petersburg, Fla., Nov. 23, aged 77.

Bachmann, George Ⓜ Atlanta, Ga.; born in Mulhouse, Alsace, France, July 18, 1877; Jefferson Medical College of Philadelphia, 1907; at one time on the faculty of his alma mater; from 1910 to 1915 professor of physiology at Atlanta College of Physicians and Surgeons, now known as Emory University School of Medicine, where he was professor and chairman of the department of physiology from 1915 to 1947, when he became professor emeritus; served as assistant dean at Emory University School of Medicine; veteran of World War I; fellow of the American College of Physicians; member of the Phi Beta Kappa, Alpha Omega Alpha, and Sigma Xi; medical director, Georgian Clinic of Georgia Commission on Alcoholism; member of the staff of the Emory University Hospital, where he died Nov. 28, aged 82.

Baldwin, John Francis Ⓜ Tenafly, N. J.; Georgetown University School of Medicine, Washington, D. C., 1932; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; veteran of World War II; member of the staff of Holy Name Hospital in Teaneck and Bergen Pines Hospital in Paramus; in 1957 received a silver jubilee award from Georgetown University; died Nov. 25, aged 52.

Bassett, Maurice Gary, Miami Beach, Fla.; Ohio State University College of Medicine, Columbus, 1926; formerly practiced in Cleveland; died Nov. 25, aged 59.

Bastian, George Leon Ⓜ Manchester, N. H.; Harvard Medical School, Boston, 1904; served on the staff of the Sacred Heart Hospital; died Nov. 20, aged 81.

Bawden, George Stephen, Springfield, Ill.; St. Louis College of Physicians and Surgeons, 1906; veteran of World War I; died Oct. 19, aged 79.

Bieberbach, Walter Daniels Ⓜ Worcester, Mass.; University of the South Medical Department, Sewanee, Tenn., 1904; specialist certified by the American Board of Urology; member of the American Urological Association; fellow of the American College of Surgeons; associated with the Worcester City Hospital, where he died Nov. 26, aged 77.

Bliss, Charles Jay Ⓜ Perry, Kan.; Kansas Medical College, Topeka, 1912; served in France during World War I; formerly served as Jefferson County health officer and a member of the Perry city council and board of education; died in Topeka Nov. 24, aged 78.

Bramkamp, Allan Lewis Ⓜ Banning, Calif.; Medical College of Ohio, Cincinnati, 1899; veteran of World War I; at one time associated with the Indian Service; died Nov. 14, aged 86.

Brenner, Franklin Theodore Ⓜ Quincy, Ill.; Rush Medical College, Chicago, 1895; member of the Industrial Medical Association; fellow of the American College of Surgeons; for many years on the staffs of the Blessing Hospital and St. Mary's Hospital; died Nov. 12, aged 88.

Briscoe, Clarence Elbridge Ⓜ New Albany, Ind.; Kentucky School of Medicine, Louisville, 1903; past-president of the Floyd County Medical Society; served as county coroner; died in the Peewee Valley (Ky.) Sanitarium and Hospital Nov. 23, aged 83.

Burrill, Clarence Dean, Framingham, Mass.; College of Physicians and Surgeons, Boston, 1928; veteran of World War I; died Nov. 23, aged 70.

Calvin, Jessie Carrithers Ⓜ Fort Wayne, Ind.; Northwestern University Woman's Medical School, Chicago, 1895; died in St. Joseph's Hospital Nov. 22, aged 91.

Canfield, Albert Ⓜ Madison, Wis.; University of Minnesota Medical School, Minneapolis, 1943; served on the staff of the Mendota State Hospital; died Nov. 24, aged 43.

Charvoz, Elton Ralph Ⓜ Phoenix, Ariz.; University of California School of Medicine, San Francisco, 1916; past-president of the Maricopa County Medical Society; affiliated with St. Luke's Hospital, Memorial Hospital, St. Joseph's Hospital, and the Good Samaritan Hospital, where he died Nov. 29, aged 69.

Cohn, Irma Stern, Cleveland, Ohio; Ludwig-Maximilians Universität Medizinische Fakultät, München, Bavaria, Germany, 1922; died in the Mount Sinai Hospital Nov. 21, aged 63.

Ⓜ Indicates Member of the American Medical Association.

Duff, Alfred William, Brentwood, Pa.; University of Pittsburgh School of Medicine, 1908; veteran of World War I; served as a physician for the Pittsburgh schools; formerly associated with St. Joseph's Hospital in Pittsburgh, where he died Nov. 23, aged 73.

Ehrlich, Maximilian Charles Ⓜ Long Beach, Calif.; University of Illinois College of Medicine, Chicago, 1920; fellow of the American College of Surgeons; served on the faculty Northwestern University Medical School in Chicago, where he was for many years on the staff of the Chicago Wesley Memorial Hospital; veteran of World War II; died Nov. 22, aged 64.

Elterman, Abraham S., East Rockaway, N. Y.; University and Bellevue Hospital Medical College, New York City, 1910; member of the American Academy of General Practice; died in the Hempstead General Hospital, Hempstead, Sept. 10, aged 71.

Felner, Isidore Israel, Brooklyn; University of Edinburgh Faculty of Medicine, Scotland, 1931; interned at the Trinity Hospital; member of the American Academy of General Practice; died Nov. 10, aged 53.

Ferrell, James Carlton Ⓜ Reno, Nev.; Chicago College of Medicine and Surgery, 1910; also a dentist; for many years superintendent of the Nevada Hospital for Mental Diseases; for 12 years member of the Churchill County Board of Commissioners; died Nov. 29, aged 87.

Gardner, Isadore Kenneth Ⓜ Pittsburgh; University of Pittsburgh School of Medicine, 1921; member of the Association of Life Insurance Medical Directors of America; served as associate medical director of the Lincoln Life Insurance Company; died in the Montefiore Hospital Nov. 21, aged 63.

Guthrie, Austin Lee, Oklahoma City, Okla.; Medical College of Ohio, Cincinnati, 1907; served on the faculty of the University of Oklahoma School of Medicine; veteran of World War I; died in St. Anthony Hospital Nov. 25, aged 76.

Hardy, John Walter Ⓜ Butte, Mont.; Miami Medical College, Cincinnati, 1891; died in Mendon, Mo., Nov. 25; aged 97.

Harris, Joshua Harley Ⓜ Memphis, Tenn.; Northwestern University Medical School, Chicago, 1918; specialist certified by the American Board of Ootolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; on the staffs of John Gaston Hospital, St. Joseph Hospital, and the Methodist Hospital, where he died Nov. 29, aged 69.

Hayden, Walter George Ⓜ Toms River, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1911; past-president of the Ocean County Medical Society, of which he was formerly secretary and treasurer; from 1940 to 1944 served on the medical board of the Selective Service; for 30 years Ocean County Jail Physician; associated with the Paul Kimball Hospital in Lakewood and the Point Pleasant (N. J.) Hospital; died Nov. 20, aged 71.

Holm, Charles Robert Ⓜ Hastings, Neb.; University of Nebraska College of Medicine, Omaha, 1946; interned at Santa Barbara Cottage Hospital in Santa Barbara, Calif., where he was associated with St. Francis Hospital; for two years in military service; died Nov. 5, aged 46.

Holmes, Lemuel I. Ⓜ Miller, Mo.; University of Louisville (Ky.) Medical Department, 1910; died Nov. 26, aged 77.

Huml, Anton Peter, Lake Geneva, Wis.; Marquette University School of Medicine, Milwaukee, 1938; interned at St. Elizabeth's Hospital in Youngstown, Ohio; served a residency at Methodist Hospital of Central Illinois in Peoria; veteran of World War II; died in the Veterans Administration Hospital, Tomah, Nov. 21, aged 47.

Hutchison, James Elder Ⓜ West Hartford, Conn.; Johns Hopkins University School of Medicine. Baltimore, 1914; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; veteran of World War I; consultant in internal medicine, Manchester (Conn.) Hospital and the Institute of Living in Hartford; visiting physician, Hartford (Conn.) Hospital, where he died Nov. 21, aged 70.

Iuler, Carl William Ⓜ Columbus, Ohio; Ohio State University College of Medicine, Columbus, 1926; on the staff of the Mercy Hospital; died Nov. 3, aged 61.

James, Jasper Milton Ⓜ Henning, Ill.; Washington University School of Medicine, St. Louis, 1905; past-president of the Vermilion County Medical Society; died in the Lake View Hospital in Danville, Nov. 20, aged 82.

Jones, Fred Durgin, Springfield, Mass.; Tufts College Medical School, Boston, 1913; also a pharmacist; specialist certified by the American Board of Pathology; for many years medical examiner for the Second Hampden District; chief pathologist at Springfield Hospital, Wesson Memorial Hospital, and Wesson Maternity Hospital; consulting pathologist at the Holyoke (Mass.) Hospital and the Cooley Dickinson Hospital in Northampton; died Nov. 21, aged 75.

Kennedy, Paul Bernard, Hamden, Conn.; Bellevue Hospital Medical College, New York City, 1896; died in Shelton Nov. 25, aged 86.

Ketchum, Philip Vial, Palo Alto, Calif.; Fort Wayne (Ind.) College of Medicine, 1902; served as health officer of Laramie County and Cheyenne, Wyo.; died in the Veterans Administration Hospital, San Francisco, Nov. 24, aged 86.

Kionka, Paul B. Ⓜ Melrose Park, Ill.; Bennett Medical College, Chicago, 1893; died in the Westlake Hospital Nov. 9, aged 88.

Klepetar, Minna-Marie, Delhi, N. Y.; Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, 1939; died in the Memorial Hospital, New York City, Nov. 8, aged 45.

Knaggs, Charles Warren Ⓜ Detroit; Detroit College of Medicine, 1903; died Nov. 21, aged 82.

Knowlton, Charles Colby Ⓜ Ellsworth, Maine; Harvard Medical School, Boston, 1911; past-president of the Hancock County Medical Society; served as a member of the state board of medical examiners; died in Bangor Nov. 23, aged 73.

Kuhn, Jerald Nelson Ⓜ Springville, N. Y.; University of Buffalo School of Medicine, 1941; interned at the Buffalo General Hospital; certified by the National Board of Medical Examiners; on the staffs of the Chaffee Hospital in Springville and the Buffalo General Hospital, where he died Nov. 24, aged 42.

Laughbaum, Thurman Ray Ⓜ Gainesville, Fla.; Ohio State University College of Medicine, Columbus, 1910; veteran of World War I; served in the U. S. Public Health Service during World War II; formerly health officer of Geary County, Kan., Marquette, Mich., Lake City, Mich., Madison County, Ohio, and Crawford County, Ohio; died Nov. 29, aged 75.

Lee, Harry Eugene, Houston, Texas; Meharry Medical College, Nashville, Tenn., 1902; associated with St. Elizabeth and Houston Negro hospitals; a member of the city board of health; died Nov. 17, aged 77.

Leggett, Clarence Dorsey Ⓜ Chillicothe, Ohio; Starling Medical College, Columbus, 1902; county coroner; died Nov. 16, aged 82.

Lehmacher, Frank Ⓜ Lakewood, N. J.; Columbia University College of Physicians and Surgeons, New York City, 1902; associated with the Paul Kimball Hospital, where he died Nov. 20, aged 81.

Lewis, David Hughes Ⓜ Spokane, Wash.; St. Louis University School of Medicine, 1907; past-president of the Spokane County Medical Society; fellow of the American College of Surgeons; died Nov. 20, aged 79.

Loar, Peter Andrew Ⓜ Silverton, Ore.; Kentucky School of Medicine, Louisville, 1903; past-president of the Marion Polk Counties Medical Society; for many years city health officer; long-time member of the Silverton Planning Commission; on the staff of the Silverton Hospital, where he died Nov. 18, aged 80.

McCutcheon, Thomas O'Donnell Ⓜ Upper Darby, Pa.; Medico-Chirurgical College of Philadelphia, 1909; on the staffs of the Thomas M. Fitzgerald Mercy Hospital, Darby, and the Delaware County Hospital, Drexel Hill; died Nov. 21, aged 80.

Major, Ralph Joseph Ⓜ Momence, Ill.; Loyola University School of Medicine, Chicago, 1933; interned at St. Anne's Hospital in Chicago; died Nov. 20, aged 51.

Maturi, Vincenzo E. Ⓜ Bayonne, N. J.; Universita di Napoli Facolta di Medicina e Chirurgia, Italy, 1922; member of the American Academy of General Practice; president of the medical staff of the Greenville Hospital in Jersey City, and on the staff of Bayonne Hospital; died Nov. 7, aged 61.

Michels, Julius Ⓜ Detroit; Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultät, Bonn, Prussia, Germany, 1924; died Oct. 20, aged 64.

Noehren, Alfred Henry Ⓜ Buffalo, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1905; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; past-president of the Buffalo Surgical Society and the Buffalo Academy of Medicine; served as treasurer of the Erie County Medical Society; consultant, Edward J. Meyer Memorial Hospital; medical director and consultant at the Deaconess Hospital, where he served as a member of the board of managers and where he died Nov. 14, aged 80.

Olson, Chester Jerome Ⓜ Belle Plaine, Minn.; University of Minnesota Medical School, Minneapolis, 1925; member of the American Academy of General Practice; lieutenant commander, U. S. Navy, during World War II; died in St. Mary's Hospital, Rochester, Oct. 20, aged 64.

Platz, Charles H., Fort Collins, Colo.; The Hahnemann Medical College and Hospital, Chicago, 1903; formerly practiced in Columbus, Neb., Torrington and Casper, Wyo.; past-president of the Wyoming State Medical Society, Rocky Mountain Pediatric Society, and the Larimer County (Colo.) Medical Society; on the staff of the Larimer County Hospital; died Oct. 9, aged 88.

Rafle, Philip J., Riverhead, N. Y.; University of Buffalo School of Medicine, 1926; interned at the Children's Hospital of Buffalo; specialist certified by the American Board of Preventive Medicine;

Suffolk County health commissioner and former deputy health commissioner in Cattaraugus County; at one time regional health director for New York City; first vice-president of the Suffolk Medical Society; director of the North Fork Chapter of the American Red Cross; a director of the Suffolk Tuberculosis and Public Health Association, Suffolk County Cancer Committee, Suffolk County Chapter of the National Foundation for Infantile Paralysis, and Suffolk County Council of Social Agencies, chairman of the New York State Conference of City, County and District Health Officers; member of the New York State Medical Society Committee on Public Medical Care; fellow of the American Public Health Association, New York State Academy of Preventive Medicine, and the American College of Preventive Medicine; died Oct. 13, aged 58.

Ritter, James William Ⓜ Milwaukee; Marquette University School of Medicine, Milwaukee, 1946; member of the American Academy of General Practice; on the staffs of St. Joseph and St. Michael's hospitals; died Nov. 17, aged 38.

Robertson, John Hourne Ⓜ Endicott, N. Y.; Albany (N. Y.) Medical College, 1917; veteran of World War I; on the staff of the Ideal Hospital; died in the Wilson Memorial Hospital, Binghamton, Nov. 17, aged 66.

Rodlie, Olaf Erling, Huntingdon, Pa.; Kongelige Frederiks Universitet Medisinske Fakultet, Oslo, Norway, 1894; formerly practiced in Albert Lea, Minn.; died Nov. 23, aged 91.

Rutkauskas, *Anthony Kazis,* Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1906; veteran of the Spanish-American War; died Sept. 29, aged 84.

Sage, Thomas Ⓜ Detroit; Detroit College of Medicine, 1931; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; associated with the Jennings Memorial Hospital, where he died Nov. 22, aged 58.

Edward Lewis Turner, M.D.
1900-1960

Turner, Edward Lewis Ⓜ Glenview, Ill.; born in Alton, Ill., Aug. 9, 1900; University of Pennsylvania School of Medicine, Philadelphia, 1928; interned at the University of Chicago Clinics; served a residency at Billings Hospital, Chicago; in February, 1959, named director of the A. M. A. Division of Scientific Activities, after serving as Secretary of the Council on Medical Education and Hospitals, which staff he joined in 1953; certified by the National Board of Medical Examiners; specialist certified by the American Board of Internal Medicine; for a time practiced in Bradford, Pa.; in 1945, appointed first dean of the University of Washington School of Medicine, Seattle, which he helped organize; from 1938 to 1944 president of the Meharry Medical College, Nashville, Tenn., where he served as professor and head of the department of medicine, and which he continued to serve as a trustee; at one time associated with the American University of Beirut, Syria, as head of the department of physiology, head of the department of medicine, and later as acting dean of the Medical School; past-president of the Tennessee State Anatomical Board, Tennessee State Basic Science Board, of which he was also past-vice-president; associate trustee of the University of Pennsylvania; director of the National Internship Matching Program; consultant, education and training division, Office of the Surgeon General, U. S. Army; consultant in tropical medicine to the Veterans Administration; served on the planning committee of the Second World Conference on Medical Education; fellow of the American College of Physicians; member of the Society for Experimental Biology and Medicine, Association of American Physicians, Central Society for Clinical Research, North Pacific Society of Internal Medicine, Washington State

Hospital Planning Council, Association of American Medical Colleges, of which he was vice-president in 1950-1951 and member of the executive council 1950-1953, Alpha Omega Alpha, Omicron Kappa Upsilon, and Sigma Xi; in 1955 his portrait was presented to the University of Washington at which time the Edward L. Turner Scholarship and Loan Fund for medical students was established; contributed many articles to professional journals; died in St. Francis Hospital, Evanston, Feb. 4, aged 59.

Upham, John Howell Janeway Ⓜ Columbus, Ohio; born in Trenton, N. J., Aug. 12, 1871; University of Pennsylvania School of Medicine, Philadelphia, 1894; interned at the Johns Hopkins Hospital, Baltimore; specialist certified by the American Board of Internal Medicine; served as President of the American Medical Association 1937-1938; member of the A. M. A. Judicial Council in 1922, and the Board of Trustees, 1923-1935, serving as chairman of the board from 1933 to 1935; dean of the faculty of the College of Medicine, Ohio State University, Columbus, 1927-1941, having been appointed professor of medicine in 1914; took postgraduate work at Prague, Leipzig, and Berlin, Germany; from 1902 to 1908 associate professor of medicine in Starling (Ohio) Medical College and in 1908 became professor of medicine and clinical medicine; represented the Federation of State Boards of Medical Examiners in the United States on the National Board of Medical Examiners; served on the State Medical Board of Ohio; secretary of the Ohio State Medical Association 1907-1913; formerly editor of the *Ohio State Medical Journal;* president of the state association 1914-1915, and at one time chairman of its public policy and legislation committee; in 1919 president of the Columbus Academy of Medicine; past-president of the Ohio Hospital Association; past-chairman of the Planned Parenthood Federation of America, Inc.; delivered the Emerling Lecture of the Pittsburgh Academy of Medicine in November, 1931; died Jan. 29, aged 88.

John Howell Janeway Upham, M.D.
1871-1960

Weaber, Thomas Hewitt Sr. Ⓜ Allentown, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1905; past-president of the Lehigh County Medical Society; past-vice-president of the Medical Society of the State of Pennsylvania, which in 1957 awarded him a plaque in recognition of his service of fifty years as a general practitioner in the community; for six years served on the school board; first medical examiner in the public schools in Allentown; for several terms on the Allentown Recreation Commission; chief emeritus of contagious disease section of the Allentown Hospital, where he died Oct. 31, aged 76.

Williamson, John Clement Ⓜ Dearborn, Mich.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1912; died in the Dearborn Medical Center Oct. 16, aged 75.

Wood, Frederic Hugh Ⓜ Bradenton, Fla.; Albany (N. Y.) Medical College 1944; certified by the National Board of Medical Examiners; specialist certified by the American Board of Urology; member of the American Urological Association; captain, medical corps, Army of the United States from 1946 to 1948; served on the faculty of the University of Illinois College of Medicine, Chicago; associated with the Manatee Veterans Memorial Hospital; died in Gainesville Nov. 5, aged 42.

Workman, Claude Henry Ⓜ McCormick, S. C.; Emory University School of Medicine, Atlanta, 1914; died Nov. 15, aged 71.

Zimmerman, Benjamin Arem Ⓜ New York City; Indiana University School of Medicine, Indianapolis, 1928; veteran of World War II; a senior medical officer for the New York Regional Office of the Veterans Administration; died Nov. 15, aged 60.

FOREIGN LETTERS

AUSTRIA

Noise.—At a meeting of the Society of Physicians in Vienna on Nov. 27, F. Schwetz stated that modern man is surrounded at all times by sound. If man differentiates between sound (pleasant or neutral) and noise (unpleasant) the question arises: "What is this difference based on?" To answer this question the speaker subdivided the various sound intensities into subjective grades of noise, using Lehmann's scale. Grade 1 includes 0 to 69 phons. Only the emotional state of the person determines whether he is disturbed by noise at this level, but noise of grade 2, which includes 70 to 89 phons, causes vegetative disturbances and pathological vascular reactions. Noise of grade 3, which starts at 90 phons, leads to organic lesions in the inner ear. Workers in noisy factories are exposed to the greatest risk of such damage. In Vienna and its suburbs there are about 95 such plants. A team consisting of an engineer, an industrial hygienist, and an otologist has been formed to suggest means of improving conditions in these plants. At present it has examined more than 500 workmen exposed to excessive noise.

BRAZIL

Helminthiasis.—D. F. do Amaral of São Paulo (*Brasil-med.*, vol. 73, Aug., 1959) studied the action of dithiazanine iodide on several species of parasitic worms. The drug cured 89 to 100% of patients who were infected with Strongyloides stercoralis. It eradicated the parasites in all patients infected with Enterobius vermicularis. The percentages of cures in patients with Trichuris trichiura was 78 and 87. Ascaris lumbricoides infections responded better to hexylresorcinol and piperazine derivatives than to the new drug. Dithiazanine was not effective against Schistosoma mansoni. Dithiazanine was effective in only about 40% of patients with Hymenolepis nana. Side-effects of the drug included nausea, vomiting, diarrhea, and abdominal cramps that varied in intensity and were present in practically all patients at the beginning of treatments. Administration of chlorpromazine before the ingestion of dithiazanine ameliorated these effects.

Neoplastic Cells in the Blood.—Drs. Torres and Paulino of Rio de Janeiro studied a series of 52 patients with carcinoma (*Rev. brasil. cir.* 38:1, 1959). Venous blood was withdrawn from the tumor at the time of operation. The authors always chose the widest veins. When possible the blood was centrifuged, but if it was scanty direct smears were made. The centrifuged specimens contained a higher percentage of malignant cells. In all cases smears were also made of blood from the cut surface of the tumor to facilitate recognition of the malignant cells. Of the 52 patients 14 (26.9%) showed malignant cells in the veins. The authors concluded that the dissemination of malignant tumors through the venous blood is much more prevalent than was thought, in some patients being more rapid and more severe, than through the lymphatics. Thus, it is necessary to emphasize the importance of handling the tumors as little as possible during operation, since they should be subjected to minimal trauma. Furthermore the veins should be tied as promptly as possible.

FRANCE

Rheumatic Fever.—At a meeting of the Medical Society of the Hospitals of Paris, J. Chevallier presented a comparative study on various treatments for rheumatic fever in 497 children. The drugs used were salicylates, hormones (ACTH, cortisone, hydrocortisone, and delta cortisone), and phenylbutazone. Only 183 of the children did not have clinically perceptible abnormality of the heart before the treatment. Among the patients in whom no cardiac involvement was detected during auscultation at the beginning of the treatment, the speaker observed in 25 the appearance of a slight systolic apical murmur in the first two weeks in which they had the disease. This occurred with the same frequency with all groups, regardless of the way in which the patients were treated. The murmur persisted in half the patients until the end of the attack of rheumatism and usually disappeared within the next six months. Generally, if a child was free from cardiac symptoms at the onset of the disease he had a 90% chance of remaining clinically free from them until the end of the disease, regardless of the method of treatment.

On the other hand, in 30 to 50% of 34 patients who at the onset of the disease had either a systolic or a diastolic mitral defect and were given phenylbutazone and in 31 with the same cardiac disturbances who were given delta cortisone, the same signs of improvement were heard on auscultation. A cure without valvular sequelas was observed in

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The items in these letters are contributed by regular correspondents in the various foreign countries.

25% of the patients. Patients with severe cardiac disease and those with pericarditis were given hormones. Of the 497 children 4 died. This represented a tenfold decline in the death rate since the advent of hormone therapy. The sedimentation rate returned to normal within two weeks of hormonal treatment, within five weeks of salicylate treatment, and somewhat more slowly with phenylbutazone. The latter treatment was generally discontinued after four or five weeks.

Fibremia decreased more rapidly in patients treated with hormones than in those treated with the other drugs. The leukocyte count decreased below 8,000 within three weeks with the treatment of either salicylates or phenylbutazone, but with hormonal treatment the count increased in the first eight days of treatment. This often necessitated its interruption because of the risk of a complicating infection. The sudden interruption of hormone treatment and its replacement of salicylates caused within 24 hours an abrupt fall in the leukocyte count, which fell from 20,000 to 10,000 per cubic millimeter in some patients.

The author studied the post-therapeutic rebound, which usually took place after four to six weeks of treatment. Almost the only reaction was the increase in the sedimentation rate, which amounted to 30 mm. in the first hour and occurred one or two weeks after cessation of treatment, and it returned spontaneously to normal within two or three weeks. This reaction was seen after the treatment with hormones in 67% of the patients and after treatment with salicylates in 50% of the patients, but it rarely occurred after phenylbutazone therapy. The latter drug caused a slower and more regular fall in the sedimentation rate without the rebound phenomenon. The author concluded that delta cortisone was the treatment of choice for attacks of rheumatic fever, but the dosage used varied from hospital to hospital. An increase in the dosage above a certain quantity, which is different for each patient, did not bring about a more rapid fall in the sedimentation rate.

Electrical Injuries.—R. C. François (*Encyclopédia médico-chirurgicale,* 1959) stated that in patients with injuries from electricity, resuscitation should be started within the first few minutes after the accident without waiting for the transfer of the patient to a specialized center. In 15 patients in whom resuscitation was successful it was started in less than 10 minutes in 7, within 10 to 19 minutes in 3, within 20 to 59 minutes in 4, and after 90 minutes in 1. Ventricular fibrillation represented the greatest danger, but it might be corrected by electrical or pharmacodynamic defibrillation with barium or potassium chloride. The resuscitation of persons who had injuries caused by high-voltage current required special attention. They did not always faint initially. Careful watching was necessary because shock, intracranial hypertension, and anuria might appear any time within the next 48 hours. Anuria was produced by the liberation of myohemoglobin from the affected tissues. The patient should be given carbonated water to drink, since myohemoglobin is less toxic in an alkaline medium.

ISRAEL

Genital Listeriosis.—M. Rabinovitz and co-workers (*Harefuah* 57:277, 1959) examined 33 women who had had repeated abortions. In 24 of these the causative organism was found to be Listeria monocytogenes. In three of these the micro-organisms were isolated during pregnancy and the abortion occurred in the second trimester. In seven the Listeria were isolated in the first trimester of pregnancy. These patients were treated with penicillin and sulfamethoxypyridazine, and abortion was prevented. In 14 the micro-organisms were isolated when the patient was not pregnant.

Interstitial Myocarditis in Children.—An outbreak of primary acute interstitial myocarditis in infant in the Haifa district, observed early in 1957, wa reviewed by W. Falk and co-workers (*Harefuah* 57:149, 1959). The epidemic involved 57 children between the ages of 6 and 18 months. About 2 sporadic cases had been observed in 1955 and 1956 Fifty of the 57 children died. Roentgenograms revealed a general cardiac enlargement, progressing from slight dilation to extreme globular enlargement. Pulmonary congestion and pleural effusion were observed in almost every child. Electrocardiographic tracings showed normal conduction mechanism despite severe myocardial damage. The main characteristics were sinus tachycardia, low-voltage complex, frequent peaked P waves of high amplitude, deviation of the right axis, and alterations in the S-T segment and T waves. Autopsies, performed on 49 children, confirmed the diagnosis o primary myocarditis. In spite of the negative outcome of virological studies a viral agent was believed to be responsible for the disease.

NORWAY

Tetrabenazine.—Tetrabenazine, a benzoquinolizine derivative, has a reserpine-like action. In animals i produces sedation without hypnosis, potentiate ether anesthesia, and has a relatively low toxicity In clinical experiments it has proved especially effective against psychotic symptoms such as delusions and hallucinations without causing undesirable side-effects. Odd Lingjaorde (*Nord. med* 52:1576-1578 [Oct. 29] 1959) gave tetrabenazine in maximal daily doses of 100 mg. to 25 hospitalized schizophrenics. Sixteen of them had first received reserpine and nine were given reserpine afterwards. In both groups there was improvement in about half of the patients during tetrabenazine treatment. Side-effects were transient. Some of these were probably due to the sudden withdrawal of reserpine. The author concluded that tetrabenazine was probably better than reserpine in the treatment of hospitalized schizophrenics.

SWEDEN

Atomic Radiation on Mice.—The Institute of Zoological Radiation Genetics has been opened at the Karolinska Institute in Stockholm. Most of what is known about radiologic genetics is derived from experiments with fruit flies. At the new institute experiments are made on mice, as reactions in these animals are more easily comparable to reactions in human beings. In the laboratory, chromosomes are loaded with inheritable changes through radiation of every new generation of mice. The testes of the mice are exposed to 275 r. A person living in Sweden at 30 years of age is estimated to have received 2 r. After the first radiation of the animals not one of their 400 offspring had any serious defects, but the litters of radiated animals were smaller than those of unradiated control mice.

Plasma Volume.—Simultaneous determinations of the plasma volume with high-molecular-weight dextran and with Evans blue on 60 normal subjects and on 69 patients was reported by Lennart Jacobsson (*Acta Soc. med. upsal.* 64:1-24, 1959). Two separate dextran preparations were used. The plasma volumes obtained with one were higher and with one were lower than those obtained with the Evans blue method. The presence of dextran-reacting antibodies in plasma did not seem to influence the determinations. There were some difficulties in the determination of the concentration of Evans blue in plasma which were easily avoided when the dextran method was used. Hemolysis and lipemia might introduce errors into the Evans blue method. In patients with highly icteric serums the Evans blue injected was less completely bound to the albumin, and the rapid loss of free stain caused an erroneously high estimation of plasma volume. In addition there might be a variation in the absorption of the same amount of stain in the plasma of different subjects. The occurrence of varying amounts of impurities of the different preparations also influenced the results, as the disappearance rate of the impurities from plasma was very rapid.

In some disease states the use of dextran of high molecular weight is to be preferred to the use of Evans blue for the determination of the plasma volume. Conditions in which increased permeability is present cause an overestimation of the plasma volume as determined with Evans blue or iodine-tagged albumin. This error can be reduced by the use of a dextran preparation of high molecular weight where even the lowest molecular weights can be kept at a level above that of albumin. On the intravenous injection of dextran untoward reactions appeared in a few patients. They were mild or moderate and probably did not influence the plasma volume determination. Discoloration of the skin never appears when dextran is used instead of Evans blue. Dextran is only transitorily deposited in various organs and tissues and disappears without leaving a trace. The coefficients of variation were of the same magnitude for the dextran and the Evans blue methods in the normal subjects, and from this point of view the two methods were equally accurate.

Effects of Barometric Pressures on Respiration.—C. M. Hesser and B. Holmgren (*Acta physiol. scandinav.* 47:28-43, 1959) studied the effects of raised barometric pressures on the respiratory systems of eight healthy patients at rest in a compression chamber. They used 100% O_2, and 5% O_2 in N_2 at various ambient pressures. With increasing ambient pressure (up to 4 G) respiration became progressively slower and deeper. The reduction in respiratory rate and the increase in tidal volume were caused mainly by the increase in gas density and hence in breathing resistance and to a lesser extent by the concomitant increase in oxygen tension.

When ambient pressure was increased from 1 to 4 G the respiratory minute volume gradually decreased and then increased slightly. The gradual decrease was caused partly by the increasing breathing resistance and partly by the removal of chemoreflex drives due to the concomitant increase in oxygen tension. The reduction in minute volume at 4 G was probably due to the increase breathing resistance. At 4 G the calculated effective alveolar ventilation was somewhat increased. The authors concluded that this increase occurred because the stimulating effect of high oxygen tension on respiration was greater than the suppressing effect on respiration of increased breathing resistance. Functional dead space volume showed no consistent difference in any of the conditions studied, which confirmed the conclusion of other investigators that the volume of the dead space is independent of the inspired oxygen tension and the density of the inhaled gas.

At 4 G the dead space/tidal volume ration was decreased as a consequence of an unaltered dead space volume and an increased tidal volume. Raising the ambient pressure to 4 G caused no consistent change in the respiratory exchange ratio, which suggested that no important interference with the pulmonary gas exchange occurred, even when the density of the inhaled gases was increased four times. Expiratory reserve volume showed no significant change in any of the conditions studied, which suggested that the long volume at the midrespiratory level increased with raising ambient pressure, since the tidal volume then increased. Nitrogen at pressures of 3 or 4 G exerted little, if any, depressant action on respiration, no matter whether the oxygen tension was normal or elevated.

Estriol.—N. E. Borglin (*Acta obst. et gynec. scandinav.* 38:157-171, 1959) studied the effect of estriol on a series of 75 patients, mostly postmenopausal. The drug increased the vascularization of vaginal mucosa. The cervical mucus increased in quantity, became watery, and resembled that associated with ovulation. It crystallized with a typical palm leaf pattern. In patients with uterine prolapse the descent of the uterus and vaginal walls decreased, and if the dose of estriol was too large, the prolapse was likely to retract so much as to cause technical difficulties at operation. There was a slight change in the cytological findings with an increased number of vaginal cornified cells and a decreased number of basal cells. The effect suggested a moderate estrogenic effect.

Histologically, there was a thickening of the epithelium with distinctly outlined cell layers, an increased number of basal cells, and rapid regeneration. The submucosa became edematous and loose with increased vascularity, while the cervical canal proliferated and became wider. The glandular epithelium appeared to be in a state of secretory activity. The endometrium increased in thickness. The basal layers showed an increased number of glands which in the functional layer were cystic and dilated, while the stroma was loose. No endometrial bleeding was observed. In many patients the endometrium responded only slightly. The effect of estriol on repair operation, the postoperative course, and such complications as bleeding, wound disruption, urinary tract infections, and retention of urine were comparable with the effect of other estrogens. The author concluded that estriol was an excellent drug for treating postmenopausal prolapse.

Effect of Relaxin on the Duration of Labor.—Engström and Wiqvist (*Acta obst. et gynec. scandinav.* 38:172-180, 1959) studied a series of 130 multiparas at or near term in whom labor was induced by oxytocin injection, the most frequent indication being Rh-sensitization. The fetus with the head presenting was alive at the time of commencement of the oxytocin drip in all cases. Thirty patients were given relaxin and oxytocin, and 100 received oxytocin alone. The latter were used as controls. The latent phase (the interval between starting the oxytocin drip and the commencement of regular uterine contractions) was significantly prolonged in the group treated with relaxin and oxytocin. In this group the duration of the average latent phase was 4.93 hours; it was 3.01 hours in the controls.

The first stage of labor was defined as the interval between the commencement of regular contractions and full dilatation of the cervix, while the second stage was defined as the interval between full dilatation of the cervix and delivery. In the present series there was no significant difference between the two groups in the duration of the first and second stages of labor, but in the group treated with relaxin and oxytocin a slight tendency for relaxin to shorten the second stage was observed. In the control group a smaller quantity of oxytocin solution was required. The authors concluded that when true labor pains had started relaxin might facilitate dilatation of the cervix, which would result in acceleration of the first and second stage.

Surgical Treatment of Focal Epilepsy.—Modern surgical treatment of focal epilepsy offers special anesthesiological problems because during the operations it is necessary to establish contact with the patients and to record the electrical activity of the cortex. Regional anesthesia during the craniotomy was customarily used. While this method did not interfere with the electrical activity of the cortex and permitted communication with a fully conscious patient, the patient had to lie in a fixed and rather uncomfortable position during a long and tedious operation. Furthermore it was difficult and sometimes impossible to prevent pain. While certain of these disadvantages might be overcome by premedication with morphine and barbiturates, this involved the risk of depressing respiration and more specifically of interference with the electrical activity of the cortex.

D. H. Ingvar and co-workers (*Acta anaesth. scandinav.* 3:111-121, 1959) used regional anesthesia in combination with nitrous oxide administered with 25% oxygen through an endotracheal tube in 23 operations for focal epilepsy. Through a perforated double cuff on the tube a local anesthetic for the trachea could be administered repeatedly. The administration of nitrous oxide was interrupted for periods of 10 to 30 minutes in the operations during which electrocorticography was carried out. During such periods it was possible to establish contact with the patient. The periods of wakefulness were well tolerated, and no side-effects due to the presence of the endotracheal tube were observed. This procedure was not used when speech functions had to be tested specifically during the operations. A comparison with a group of 26 patients operated on under regional anesthesia showed only that the nitrous oxide procedure did not interfere with, or tend to hide, epileptogenic abnormalities in the electrocorticogram.

Clinical Trial of Secergan.—Dr. J. Tomenius (Svenska läkartidningen, Nov. 6, 1959) treated a series of 94 patients, (43 with peptic ulcer, 42 with gastritis, and 9 with functional disturbances of the intestinal tract). Of these, 48 were given secergan, a phenothiazin derivative with marked anticholinergic action, and 46 were given a placebo. Complete freedom from symptoms was achieved by 66% of those given secergan and by only 30% of those given the placebo. This difference was most marked among the patients with peptic ulcer, the figures being 70 and 30% respectively, but those with gastritis also showed the relative inferiority of the placebo. The reason that the placebo was impotent is that the patients lived in an ambulatory condition and were sheltered from the influence of psychotherapy which is always operative in a hospital atmosphere. In this test the element of confusion introduced by dieting, sedatives, and hypnotics was avoided. No disagreeable side-effects, such as dryness of the mouth and throat, eye symptoms, or disturbances of micturition, followed the administration of secergan.

A Quick Test of Hearing.—In 1951 in the northern part of Sweden, 32,885 schoolchildren underwent the old clinical test of listening to the spoken word at a certain distance. Among them 218, or 0.7%, were found to have defective hearing, yet routine tests throughout Sweden in recent years with an audiometer have shown with remarkable uniformity that 3.3% of the schoolchildren suffer from defects of hearing serious enough to interfere with learning. The discovery of these defects usually came as a surprise to pupil, teacher, and parents. As Dr. L. Holmgren (Svenska läkartidningen, Nov. 6, 1959) pointed out, the general practitioner cannot be expected to equip himself with the type of audiometer used by the Audiological Laboratory of the Karolinska Hospital for various tests, but a handy substitute for this instrument is the Quick-Check Audiometer which has been in use in Sweden during the past year and which is supplied with a miniature electric battery capable of lasting a year when used economically (only a few seconds for each test).

Azacon in Psychiatry.—At a mental hospital in Malmö, 140 men suffering from schizophrenia or other psychiatric ailments were treated with azacon, whose chemical structure somewhat resembles that of chlorpromazine but whose clinical effect differs from that of this drug. Commenting on these cases Drs. Uddenberg and Lundgren (Svenska läkartidningen, Nov. 20, 1959) stated that 73 of the patients suffered from latent schizophrenia, 21 from active schizophrenia, and 11 from psychoses due to injuries to the brain. The rest had other psychiatric ailments. Azacon was usually given by mouth, the dosage ranging from 40 mg. thrice daily to 80 mg. three or four times daily. When the patients did not respond to the larger doses, the drug was abandoned in favor of chlorpromazine. In Germany, however, good results were obtained with up to 1 Gm. of azacon daily. Though azacon may not deserve to replace chlorpromazine altogether, it possesses the advantage of not provoking the parkinsonism or lassitude to which the recipients of chlorpromazine are liable. Some time before a patient is discharged it is well to start giving him azacon rather than chlorpromazine in order to facilitate his adaptation to life outside the hospital. The postchlorpromazine lack of initiative can thus be avoided. The side-effects of azacon are on the whole harmless and transient.

UNITED KINGDOM

Speeding by Doctors.—A physician successfully appealed against sentence on his conviction for speeding while on an emergency call. He was fined 12 dollars by Lancashire magistrates and had his driving license endorsed after pleading guilty of speeding at 48 miles an hour in an area restricted to 30 miles. The magistrates did not consider that the circumstances constituted a special reason for not recording a conviction. Under the law speeding may be permitted under exceptional circumstances, for example by the police or by fire engines. The Appeals Committee, however, reversed the magistrates' decision and held that speeding by the doctor called to an urgent case did in fact constitute an exceptional circumstance. Legal commentators pointed out that this decision must not be taken as a carte blanche for speeding by doctors when called to an emergency. Each case must be decided on its own merits. The degree of urgency of the call must be balanced against the degree of danger to the public in speeding. As one commentator pointed out, there is no benefit in killing a pedestrian to save a patient.

Antibiotics for Bronchitis.—Chronic bronchitis is a major cause of industrial invalidism and results in the annual loss of 22 million male working days. Murdoch and colleagues studied the therapeutic effects of the continuous treatment of bronchitics during the winter months with oxytetracycline and tetracycline (*Brit. M. J.* 2:1277, 1959). A series of 98 bronchitics were given capsules containing either a mixture of 167 mg. of tetracycline and 83 mg. of oleandomycin or 250 mg. of oxytetracycline while the control patients had capsules containing an inert powder. Four capsules a day were given. Progress was assessed from bacteriological examination of sputum and nasal swabs and from clinical response, the patient being graded as improved, unchanged, or worse. The results of the trial clearly showed that men with chronic bronchitis benefited from continuous daily treatment during the winter months with one of the tetracyclines. This was found to be particularly the case in elderly bronchitics with advanced disease. The absence of recurrent winter invalidism and consequent loss of time from work was a noticeable advantage of continuous antibiotic therapy, as shown by the comparison of days lost by treated as compared with untreated patients. It was concluded that the best time to start treatment is in the autumn. The occurrence of an acute exacerbation of bronchitis in those patients receiving the inert capsules led to their withdrawal from the trial.

The degree of purulence of the sputum was found to be a useful guide to the efficacy of antibiotic treatment, since there was good correlation between it, the clinical state of the patient, and the presence of Hemophilus influenzae and Diplococcus pneumoniae in the sputum. The dose of antibiotic was adjusted so that the sputum remained mucoid. This was about 250 mg. four times a day. Looseness of the stools was troublesome in about 33% of the patients, but in none was it associated with a significant change in the intestinal flora. Additional confirmation of the role of H. influenzae in chronic bronchitis was the demonstration of high antibody titers in the serums of patients who regularly harbored this organism in their sputums. It was suggested that H. influenzae has the invasive properties which lead to the inflammatory destruction of bronchopulmonary tissue demonstrable in chronic bronchitis. Bronchoscopic aspirates yielded H. influenzae in most patients with purulent sputum.

Some of the strains of Staphylococcus aureus isolated during and after treatment were resistant to the antibiotics used, but this did not constitute a real danger. Gross disturbance of normal surface flora of the respiratory and intestinal tracts was not observed. It was found practicable to treat the patients on an outpatient or domiciliary basis, which had the advantage of lower cost than hospital treatment. To avoid the dangers of superinfection with antibiotic-resistant and often highly virulent microorganisms it was recommended that if exacerbations should arise the patient is better treated at home rather than in the hospital. One serious consideration was the cost of such antibiotic treatment, which is about 180 dollars for six months, or 7 dollars a week, if the patient is treated by his own doctor. This compares favorably with the cost of hospitalization, which is nearly 62 dollars a week in a good teaching hospital, and the additional charge on the state for sickness benefit and the financial loss to industry.

Shortage of Surgeons.—A London consultant pointed out in the *Daily Telegraph* of Dec. 18 that on Dec. 2 at a large London hospital of good reputation, there were four applicants for a post of house surgeon to three surgeons with general and special surgical interests. The applicants were one Englishwoman and three men from Ghana, Jordan, and Siam respectively. There was no Englisl male applicant. The difficulty experienced in recen years, at a small hospital some 10 miles from London, of getting a caucasoid male house surgeon c resident surgical officer is now becoming mor common in London. Such a lack of homebred, c even Canadian, South African, or New Zealanc applicants is a new phenomenon and augurs ill fc the future. The reason for this situation may b sought in the cavalier treatment of medical deputations to the Ministry of Health and in the psychological and financial pin-pricks and gener atmosphere of denigration to which the medic profession has of late been subjected. In medicin there is often a family tradition, but physicians n longer urge their sons or daughters to enter th profession.

Midwives Dying Out.—Maternity work in Gre Britain is largely in the hands of midwives. A mi wife, after four years' training, can now start $1,610 a year (31 dollars a week). A district mi wife who has the responsibility of life and death her hands and is on duty 144 hours a week inclu ing Christmas and other holidays, must often li in the most austere circumstances. Income ta superannuation, and insurance all must be paid o of her inadequate salary. This niggardly mann of treating the women who bring 750,000 babies year into the world is having the inevitable resu Fewer persons are becoming midwives.

In 1959 only 16,445 midwives were registered practicing, or nearly 500 less than in 1958. Th number of district midwives was 7,790, or near 200 less than in 1958. About 3,000 midwives qual fied last year, but 3,500 left Britain. Kenya ar New Guinea offered posts at 62 dollars a wee Vancouver offered 347 dollars a month for a 40-hou week; and Newfoundland offered 53 dollars week plus full maintenance. In Britain there are 1,0 closed beds in hospitals due to the shortage midwives.

Television Neck.—A condition known as "televisio neck" may follow watching television from a cha of the wrong height, according to the *Lancet* Dec. 26. The author warns that to sit endless watching TV brings a risk of illness, includin heart trouble, but the hazard is small and shoul not be exaggerated. Simple syncope is not unusu when surgical procedures are shown, and tr angina pectoris may be provoked by some pr grams. Prolonged immobility in an awkward po ture entails a risk of venous thrombosis. On medical writer recommends that viewers move fro their chairs at least once an hour. Flickering of the set has been known to initiate a fit in a susceptible epileptic.

CORRESPONDENCE

STATISTICS AND TOBACCO

To the Editor:—I am shocked by your editorial on smoking and lung cancer. Could you define the kind of evidence which you would accept as showing a relationship between cigarette smoking and ung cancer?

DAVID D. RUTSTEIN, M.D.
Department of Preventive Medicine
Harvard University Medical School
Boston 15.

See the following communication.—ED.

To the Editor: In THE JOURNAL, Nov. 28, 1959, page 1829, appeared a statement[1] of the surgeon general of the U. S. Public Health Service, Dr. L. E. Burney, on smoking and lung cancer, which has been widely interpreted in the editorial press as an authoritative pronouncement of the Public Health Service and as a definitive opinion on the scientific issues involved in that controversial subject. I beg to present some reasons for doubting each of these evaluations.

In general, the article is characterized by an imprecision of language and thought that renders inaccurate almost every important point it deals with. In particular, it contains some frank errors of omission and commission which are misleading with regard to the basic questions at issue. On page 1830 it is stated, "Berkson . . . noted that the data of Hammond and Horn and of Doll and Hill point not only to an association between smoking and lung cancer but also to a wide variety of diseases never presumed to have the same etiology as cancer." The reference is to a communication[2] that was written shortly after the publication of the two reports with which it deals and before any statistics from the large prospective study being conducted by Dorn for the Public Health Service were issued. I did not merely note the presence of an "association" of smoking with a wide variety of diseases. I emphasized that only about 14% of the "excess deaths" reflected in the higher death rate of smokers compared to nonsmokers were due to lung cancer, while 86% were due to causes other than lung cancer. Fairly soon after the publication of some statistics from Dorn's study, I presented an analysis[3] disclosing similar findings in Dorn's data, which showed only 12.7% of the excess deaths to be due to lung cancer, 9% due to other cancer, and 78.3% due to other causes.

Burney's article deals meagerly with Dorn's reports and mentions only some findings with respect to lung cancer. Taken together with the omission of reference to my second report, this presentation can easily mislead the reader to believe that my quoted observations, referring to the studies of Doll and Hill and of Hammond and Horn, do not apply to the study of Dorn, when, in fact, the opposite is true. Similarly, his summary of the report of Hammond and Horn mentions only some data on the relation of smoking to deaths from lung cancer in face of the fact that the report[4] itself says, "A total of 7,316 deaths occurred among regular cigarette smokers, an excess of 2,665. . . . Coronary disease accounted for 51.2 per cent. . . , lung cancer . . . for 13.5 per cent, and cancer of other sites likewise 13.5 per cent. . . . The most important finding of this study was the high degree of association between cigarette smoking and total death rate."

The finding of associations of smoking with all classes of disease, not only or even chiefly with lung cancer, is of central importance for an interpretation of the biological significance, if any, of these statistical studies,[5] and Burney's presentation, which obscures them, could leave an impression of misrepresentation.

On page 1833 an argument for smoking as a cause of lung cancer is advanced on the basis of the lower mortality from lung cancer among women, which appears to have made a strong favorable impression on some editors.[6] Here it is stated that "nonsmoking women have about the same lung cancer death rate as nonsmoking men," which, almost certainly, is not true. The death rate for men is greater than that for women, not only for cancer of the lung but for cancer of almost every organ that is comparable in the two sexes and for virtually every noncancerous disease also.[7] The higher general mortality of the male than the female is characteristic of the entire animal kingdom; it is usually related by biologists[8] to the presence of two X chromosomes in the cell of the female and only one in the male, not to smoking. One would not know, reading this portion of the surgeon general's statement, that a special study[9] devoted to the sex ratios of mortality from lung cancer had been published, with conclusions different from his, for it is not mentioned in his text or references.

On page 1834 one reads, "In the study of Leuchtenberger and co-workers . . . mice were exposed to cigarette smoke and examined after varying periods, the longest being 200 days. In most animals the bronchial epithelium showed inflammation and simple and atypical basal cell hyperplasia. Passey . . . stated, however, 'Our failure during the past five years [recorded in previous publications] to induce lung tumours in mice, rats, and hamsters by exposure to strong concentrations of cigarette smoke is a striking negative result.' " The impression one gets from these passages is that the results of Leuchtenberger and associates contradict, or at least mitigate, those of Passey, who obtained negative results in attempts to produce lung cancer experimentally by exposure to smoking.

The report of Leuchtenberger and co-workers[10] referred to in the passage is an early, preliminary one. A later report of this work was given by Leuchtenberger and others at the International Cancer Congress in London, in July, 1958. The summary of this report[11] reads as follows.

> 1. There is a development of a bronchitis associated with a gradual change of the normal resting epithelium to an inflammatory, proliferating, and dysplastic one ("carcinoma in situ," multifocal). *No invasive carcinoma.*
> 2. When exposure to cigarette smoke is stopped for over 3 months, the normal appearance of the bronchi suggest reversibility of bronchitis and dysplasia.
> 3. The cytochemical alterations in the bronchial epithelium also show a gradual development. . . . The cytochemical alterations are also reversible when exposure to cigarette smoke is stopped.

This later report of Leuchtenberger and others is, in content and in tone, virtually the same as Passey's, not in contrast to it.

An even less explicable lapse is Burney's failure to cite the experiments performed in the Public Health Service itself, in the laboratory of the pathologist, Dr. H. L. Stewart, in which administration of cigarette smoke to mice failed to produce lung cancer.[12]

So it is found that, in these parts of his text, Burney refers to a report of Leuchtenberger and co-workers in an equivocal way with respect to the experimental production of lung cancer by smoking, while omitting reference to a later report by the same author and others which is emphatically clear as to the failure to produce such cancers, and he omits entirely any reference to experiments with similar negative results performed in the U. S. Public Health Service laboratories.

The article is presented as a statement of the Public Health Service. When I read this I was surprised, for the following reasons. Several weeks before the article appeared, I had presented a paper[13] related to the present subject at a biometrics seminar of the Public Health Service in Bethesda, Md. The paper was technical and intended to demonstrate mathematically that some statistical methods which had been used in the analysis of the prospective studies of smoking and lung cancer were unsound, with consequent misinterpretation of the data in these studies. The talk was well attended, and I assume the audience contained a fairly large proportion of the biometricians in the Public Health Service. I did not sense, during my talk or during the discussion that followed, any disagreement with the tenor of my remarks. I recall clearly that when I said, "We should not be engaging in fine semantic efforts to demonstrate that the extremely complicated statistical evidence proves the validity of the theory that initiated these studies. Instead, we should set up investigations in large variety to find out what they mean," there was spontaneous applause, from what seemed to be the entire audience.

I spent considerable time with Dr. Dorn and with some veteran experimental workers of the Public Health Service and have corresponded with others. I cannot speak didactically of their views, but I can say that they seemed in general agreement with mine, as regards the tentative character of the evidence. Surely, I had the impression that Dorn believes that much more work in pharmacology, pathology, and other associated sciences must be done before anything definite can be said with regard to the explanation of the statistical findings. Certainly, the word "cause" does not appear in any of his writings on the subject, and he has recently expressed himself elaborately on the complexities of interpreting statistical results for their etiological significance.[14] In these circumstances, and recalling the insufficiency of Burney's reporting of Dorn's statistics, I cannot believe that Dorn reviewed or edited the statement of the surgeon general before its publication, nor can I believe that Stewart did considering that his own work was not cited, leaving aside other inaccuracies that I cannot believe him to have approved. Dr. Dorn is chief of biometrics of the National Institutes of Health and the director of its main statistical study on smoking and lung cancer. Dr. Stewart is chief of pathology and a renowned worker in the field of experimental cancer. If neither of these scientists of the Public Health Service previewed the surgeon general's article before publication, not to speak of the failure to consult many other experts in related fields on its staff, how can this article be properly designated a statement of the Public Health Service?

There is an aspect of deficiency of the surgeon general's statement that is of even more serious import than those just discussed. If the Public Health Service believes that tobacco smoke contains chemical carcinogens which cause lung cancer, then the first task of its responsible scientists is to isolate these substances in "pure culture" and to identify their chemical structure. This is the first step required by Koch's postulates for demonstration of a causative agent of a disease. It is furthermore the first step to be taken in order to use the discovery for amelioration of the disease. Since Pasteur, the isolation of a specific cause of a disease has been followed immediately by experiments to produce an immunizing agent. The Public Health Service has had appropriated for its use in a single year about 700 million dollars; about 350 million dollars has been for the National Institutes of Health, in cluding 85 million dollars for the National Cancer Institute, with about 20 million dollars allocated specifically for research in chemotherapy. How much of these considerable funds has been spent or allocated for carrying out the first steps to be taken to realize the discovery of an important cause of lung cancer? So far as I can learn, none at all. So far as I know, the only experiment on smoking in relation to lung cancer published from the Public Health Service is the negative experiment [10] that I cited above, and no work of this nature is in progress now.

As I have repeatedly pointed out, the prospective studies show more excess deaths among the smokers from other causes than from lung cancer, and these other causes are distributed among all classes of disease. If the statistical results are not spurious but reflect some real biological effect, this points to a generalized, not a local, effect. I have presented a plan [15] for an experimental epidemiologic study to explore this lead. Why has not the Public Health Service set up this experiment, or some modification of it?

Sir Ronald Fisher, who has been critical of the analysis of the English data on smoking and lung cancer,[16] early remarked, "The question seems to be a serious one; when is serious investigation going to begin?" His question is timely even now.

Joseph Berkson, M.D., D.Sc.
Mayo Clinic
Rochester, Minn.

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ELI LILLY MEDICAL RESEARCH FELLOWSHIP (SOUTH AFRICA)

To the Editor:—The attention of medical practitioners registered in South Africa, who may at present be in the United States, is drawn to the fact that applications may now be submitted for the 1960 award of the Eli Lilly Medical Research Fellowship. The fellowship is given for the purpose of medical research and is not intended for postgraduate clinical study. The net value of the fellowship is $300 per month for 12 months, plus return traveling expenses to the point of study in the United States of America. Further details can be obtained from me. The closing date for applications is April 30, 1960.

H. A. Shapiro, M.D.
Honorary Chairman: Selection Committee
Eli Lilly Medical Research Fellowship
P. O. Box 1010
Johannesburg, Union of South Africa

FAT CONTENT OF SEMEN

To the Editor:—In my busy practice, I find myself several weeks behind in reading The Journal, and it was only last night that I had an opportunity to review the Aug. 1, 1959, issue. I would like to know where the scientist who prepared the answer to the question on page 1756 of this issue obtained the caloric values for fat given.

D. S.
New York City.

I regret to state that the person who prepared the reply has been given another assignment and is not available for comment.—Ed.

MEDICAL FILM REVIEWS

The Buffering of Carbon Dioxide During Hypercapnia: 16 mm., color, sound, showing time 24 minutes. Prepared by Gabriel G. Nahas, M.D., Washington, D. C. Produced in 1959 by and procurable on loan from Research Films Section, MAVD, Walter Reed Army Institute of Research, Washington 12, D. C.

The data presented in this film are preliminary and are documentations of unconfirmed research investigation. It shows the use of a tris buffer (THAM) in treatment of hypercapnia of apneic respiration. It thoroughly describes the cardiovascular and metabolic responses of two dogs to hypercapnia, one untreated and one treated with THAM. This is followed by a short graphic summary of the results. Many small items are not fully explained and could be confusing to medical students. Because of inappropriate film cutting, pentothal appears to be injected rapidly, resulting in instantaneous anesthesia. The cannula placed in the cisterna magna was allowed to drip for some time and was never connected to the pressure transducer. The mechanism of action of the compound could have been more completely described. Dangerous side-effects from its use are not mentioned. Technically, the film is well done: however, the production is amateurish in spots. The subject should be of interest to medical students, graduate students in physiology and pharmacology, anesthesiologists, and those interested in acid-base balance as affected by respiratory disease.

A Pharmacologic Approach to the Study of the Mind: 16 mm., black and white, sound, showing time 33 minutes. Produced in 1959 by Sherman Dryer Productions, New York, for and procurable on loan from Lakeside Laboratories, Inc., 1707 E. North Ave., Milwaukee 1.

This is a series of excerpts from a conference held at the Langley Porter Clinic on the topic indicated by the film title. Ralph Gerard introduces the speakers and serves as general interlocutor. The conference was opened by Alec Simon, who commendably recommended an attitude of "healthy skepticism." Various comments on LSD and mescaline were then made by James Dille, Sidney Cohen, and others, and by Leo Abood on his studies of the various piperadyl benzylates. These reports revealed wide disagreement as to whether (*a*) these "psychotomimetic" drugs cause "true" or "merely toxic" psychoses, or whether (*b*) they are of diagnostic or therapeutic value. The conference continued with a note by J. Kinross-Wright on the favorable effects of beta-phenylisopropyl hydrazine hydrochloride (Catron) on depressive reactions, and with predictions by J. Pomeranz, Nathan Kline, and others to the effect that such monoamino-oxidase inhibitors may largely replace electroshock therapy in certain patients. Dr. Gerard closed the conference on the same healthy note with which it opened: a healthy skepticism. More pictures of patients would have been an improvement. The kinescope recording used in the film is poor. The film may be of interest to a specialized audience of psychiatrists or psychopharmacologists. It is not suitable for viewing by general medical audiences.

NEW FILMS ADDED TO A. M. A. MOTION PICTURE LIBRARY

Open Fractures: 16 mm., color, sound, showing time 24 minutes. Produced in 1959 by Churchill-Wexler Film Productions for the Veterans Administration. Prepared by William A. Larmon, M.D., Chicago. Procurable on purchase from Churchill-Wexler Film Productions, 801 N. Seward St., Los Angeles 38, or on loan (service charge $2) from Motion Picture Library, American Medical Association, 535 N. Dearborn St., Chicago 10.

The basic principles underlying the treatment of open fractures are illustrated in this film. It shows a typical patient, with a fractured tibia, being given emergency treatment at the site of an automobile accident. Further treatment in the emergency room of the hospital, surgery, and postoperative care are shown in detail. Definitive surgery is demonstrated in the operating room in two different patients, one treated by the open method and one by primary closure. It is an exceptional film on open fractures. The content is excellent and scientifically accurate. The photography, narration, and general organization are good. Animation is used extensively to demonstrate procedures, both in concept and practice. The film has broad application and is recommended to general practitioners and the medical profession as a group. It can also be used to advantage by interns and residents and is highly recommended to medical students, especially in the junior and senior years.

Mouth to Mouth Resuscitation for Respiratory Emergencies: 16 mm., color, sound, showing time 18 minutes. Prepared in 1958 by Archer S. Gordon, M.D., Los Angeles. Procurable on loan (service charge $2) from Motion Picture Library, American Medical Association, 535 N. Dearborn St., Chicago 10.

This film details the physiological requirements for effective artificial respiration and outlines the experimental and [illegible] of the development of [illegible]. The subject of resuscitation is concisely covered and the film demonstrates the mouth-to-mouth method and three manipulative methods which have been effective. A complete review of this film appeared in THE JOURNAL, Oct. 31, 1959, page 1253.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Chlorothiazide as a Diuretic Agent in the Treatment of Congestive Cardiac Insufficiency. A. Dräyer B., P. Blanco H. and S. Henriquez E. Arch. Inst. cardiol. Mexico 29:533-545 (Sept.-Oct.) 1959 (In Spanish) [Mexico, D. F.].

Twenty-eight patients with congestive cardiac insufficiency of varied etiology were treated with chlorothiazide for an average period of one month in the cardiology department of the University Hospital of Caracas, Venezuela. The patients' ages ranged from 12 to 65 years. The daily dose of chlorothiazide was 1 Gm. for each patient (500 mg. every 12 hours). The treatment was preceded by an observation period of one week, during which the patients were kept on a low-salt diet with a constant sodium and potassium content. The cardiac insufficiency was considered to be compensated when the venous pressure, both at rest and after hepatic compression, was within the normal limits.

The results of the therapy were excellent (decrease of the venous pressure to normal values, total disappearance of hepatic congestion and of the clinical manifestations of cardiac insufficiency) in 15 patients (53.75%). In 10 patients (35.75%) the results were good, with the venous pressure remaining somewhat higher than the normal values. In only 3 patients was the treatment a failure. In one of these patients the administration of prednisone (30 mg. on the first day, followed by a daily dose of 20 mg. during 23 days) produced an increase in the urinary output and in the excretion of sodium and potassium, resulting in compensation of the cardiac insufficiency. The most constant and important electrolytic change was the increase in the excretion of potassium, without the amount consumed in the daily diet being exceeded. In spite of this ratio, however, hypopotassemia was observed in 19 patients (67.8%). The patients who were followed up and were kept under chlorothiazide therapy continued to be free from edema and symptoms of cardiac insufficiency. Unfavorable reactions were few and in no case caused interruption of the treatment or decrease in the dosage. The authors believe that chlorothiazide is as effective as the mercurial diuretic agents, is better tolerated, and is easier to administer. Its effects are more uniform; its side-effects are fewer and less marked.

Congenital Defects in Bilirubin Metabolism as Seen in the Adult. L. Schiff and B. H. Billing. Gastroenterology 37:595-602 (Nov.) 1959 [Baltimore].

The authors differentiate 3 types of congenital defects in bilirubin metabolism in adults. First, they discuss constitutional hepatic dysfunction (Gilbert's disease), which is characterized by elevation only of free bilirubin level in the serum, either as a result of deficiency of a hepatic conjugating enzyme or, more probably, as a result of impaired hepatocellular uptake of bilirubin from the plasma. In the second type of disorder, chronic idiopathic jaundice (Dubin-Johnson syndrome), the levels of free bilirubin and conjugated bilirubin are elevated in the serum, and pigment is found in the liver. The third type of disorder, which has been described only recently, is chronic familial nonhemolytic jaundice with conjugated bilirubin in the serum. This syndrome is characterized by the presence of conjugated as well as free bilirubin in the plasma, the values for which may fluctuate. Bile pigments can be detected in the urine, provided that the level of conjugated pigments in the plasma is sufficiently high. Diminished conjugation by the hepatic cells, as well as a defect in excretion, is assumed. These disorders are of interest and importance to both clinician and investigator. To the clinician, recognition avoids treatment for the wrong diagnosis of hepatitis or biliary tract disease and provides a basis for reassurance and a favorable prognosis. To the investigator, the mechanisms of these disorders are challenging, and their study should advance knowledge of liver function and liver disease.

Tuberculosis in Women. C. Palenzona. Minerva med. 50:3271-3274 (Oct. 17) 1959 (In Italian) [Turin, Italy].

The author made a study of the incidence of tuberculosis among women as compared with that among men. The study is based on observations by the author and by other workers in Italy, France,

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The place of publication of the periodical appears in brackets preceding each abstract.

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and Switzerland. In the past the incidence of tuberculosis was highest in the puberal age, and at that time more girls than youths died of it. Presently, in civilized countries, the primary infection has gradually tended to take place later in life. This fact explains the current higher incidence of tuberculosis among men than among women of all ages except in adolescence. At the present, the mortality rate among those dying of extrapulmonary tuberculosis in Italy is approximately equal in both sexes, but the mortality rate of all varieties of tuberculosis is more than double among men. Women are more cooperative than men in participating in treatment of the disease, which circumstance accounts for a slightly better prognosis in women than in men.

Pregnancy, labor, and puerperium are no longer adverse conditions for a woman with tuberculosis, provided that the patient is hospitalized. The author reports that during the past 4 years 7 pregnant women with active tuberculosis, who were hospitalized at the clinic with which he is associated, delivered healthy infants. Six of the women were discharged as cured within a few months after the delivery, but one patient died 3 years after childbirth. The author performs a pneumoperitoneum if cavities in a woman after delivery remain refractory to chemotherapy. Vocational readjustment, if necessary after completion of the treatment for tuberculosis, is easier for a woman than a man because, by tradition, women in Italy rarely perform heavy manual work.

Congenital Deficiency of Proconvertin: A Clinical and Laboratory Report. S. P. Miller. Blood **14**:1322-1338 (Dec.) 1959 [New York].

The authors report a case of congenital deficiency of proconvertin (factor VII) in a 2-year-old Hopi Indian boy, who had a moderately severe hemorrhagic tendency since birth, but essentially normal intrinsic coagulation despite the absence of detectable levels of proconvertin by the methods currently available. In 10 cases collected from the literature, a deficiency of the identical factor missing in this patient appeared to be present. Thus, the case of this patient is the 11th case of "pure" proconvertin deficiency and the second reported in the American literature. The patient's plasma reacted normally to plasma thromboplastin generated in the normal incubation mixture, and normal plasma reacted normally to the patient's thromboplastin. The patient's own thromboplastin gave a normal reaction when subtested against the patient's plasma. Abnormal results were obtained when the patient's coagulation was studied in the presence of tissue extracts. The one-stage assays utilizing brain thromboplastin were markedly abnormal in test systems sensitive to a deficiency of proconvertin. These included the one-stage prothrombin time of Quick and the proconvertin assay. An accompanying mild deficiency of prothrombin was suggested by the results of some tests.

The concept that the role of proconvertin in hemostasis is primarily as a co-thromboplastin is supported by the clinical and laboratory studies carried out in this patient. The differentiation of "pure" proconvertin deficiency from other cases of deficiencies of "serum factors," particularly deficiency of the Stuart factor, has been discussed. A total of 65 cases, labeled deficiency of serum prothrombin conversion accelerator (SPCA), proconvertin, factor VII, or Stuart-Prower factor, have been collected from the literature and reviewed.

Hyperbilirubinemia Due to an Alternate Path of Bilirubin Production. L. G. Israels, H. J. Suderman and S. E. Ritzmann. Am. J. Med. **27**:693-702 (Nov.) 1959 [New York].

The authors report on 4 cases of hyperbilirubinemia, which occurred in 2 families from southern Manitoba, Canada. Three patients (2 brothers and a sister) belonged to the same family and had developed jaundice for the first time at puberty. Their father also had had an episode of jaundice at the age of 12 years. One brother and the sister underwent splenectomy. In both patients the spleen weighed approximately 350 Gm.; histologically, the pulp and sinuses contained prominent endothelial cells. Biopsy specimens of the liver, taken from both patients, showed a heavy infiltration, a brown pigment occurring as granules of irregular shape and size in the hepatic parenchymal cells, and being primarily concentrated in the periphery. The fourth patient was a 40-year-old woman, with no direct kinship to the other 3 patients. This woman had been asymptomatic until the age of 18, when she was found to be jaundiced and anemic. At 31 she developed splenomegaly. One year later she was hospitalized, and a diagnosis of spherocytic anemia was established. The removed spleen was congested, and the endothelial cells lining the sinuses were prominent. There was no excessive deposition of iron. The hemoglobin level rose, the serum bilirubin level fell, and the jaundice was less marked after the operation. The patient still tired easily, although otherwise she was well.

The patients reported on were free from antecedent hepatitis, and all exhibited some features of congenital spherocytosis, such as jaundice, splenomegaly, spherocytes in the peripheral blood, and an increased osmotic fragility on incubation. There were also some marked differences from congenital spherocytosis. Autohemolysis and mechanical fragility were normal. After the splenectomy, the survival of radioactive sodium chromate (Cr^{51}) was extended to normal, the serum bilirubin value was reduced, and the urine urobilinogen dropped to one-half of the preoperative level, while an appreciable hyperbilirubinemia persisted, together with reticulosis and normoblastic marrow. The total urobilinogen output remained high in the presence of a normal Cr^{51} red blood cell survival time. The authors suggest that the excess bilirubin had its source in the marrow erythrocytes or their precursors, either by their destruction or by their synhesis of bilirubin directly from heme or its tetrapyrrole antecedents. The occurrence of 3 cases of hyperbilirubinemia with the same features in the ame family indicates that it is a familial disease, probably representing an autosomal recessive characteristic.

A Familial Study in Idiopathic Hemochromatosis. T. H. Bothwell, I. Cohen and others. Am. J. Med. 27:730-738 (Nov.) 1959 [New York].

Fifty-two immediate relatives (parents, siblings, and children) of 6 patients with idiopathic hemochromatosis were observed. The diagnosis of hemochromatosis was confirmed at autopsy in 5 patients and by liver biopsy in 1. Each of the relatives was examined clinically, and determination of fasting serum iron was performed on all subjects, except 5 young children. Liver biopsies were performed on those showing persistently raised serum iron evels. Of 19 siblings investigated, 3 manifested the clinical symptoms of the disease, and 5 showed varying degrees of iron excess on liver biopsy. Six of the siblings with negative findings were under the age of 20 years and might exhibit manifestations at a later period. In one family the mother showed a persistently raised serum iron level, in spite of a normal liver biopsy. In another the father had hepatomegaly and a raised serum iron level. In 3 children of 2 patients there was evidence of the iron metabolism defect.

The results support the concept that idiopathic hemochromatosis is a familial disorder in which the absorption of excessive amounts of iron from the intestines eventually leads to a massive accumulation of iron within the body. The disease is probably the result of an autosomal genetic defect of incomplete penetrance and/or variable expressivity, which is transmitted as a Mendelian dominant trait. The practical value of familial studies in idiopathic hemochromatosis is stressed, since affected persons can thus be detected and treated during the preclinical phase of the disease.

Vitamin B_{12} and Folic Acid Metabolism in Hookworm-Infected Patients. M. Layrisse, N. Blumenfeld, I. Dugarte and M. Roche. Blood 14:1269-1279 (Dec.) 1959 [New York].

The authors report on 21 patients with severe anemia and heavy hookworm infection (groups A and B), who were hospitalized in the medical wards of Hospital Vargas and Hospital Universitario in Caracas, Venezuela, also on 5 patients with light hookworm infection who were hospitalized for symptoms distinct from anemia (group C), and on 5 noninfected patients with various degrees of iron-deficiency anemia (group D), in whom studies on folic acid and vitamin B_{12} metabolism were carried out as a part of the study of the antianemic factors in these patients. In a group of healthy laboratory workers (group E), only serum vitamin B_{12} and folic acid tests were performed. The patients of groups A and B harboring severe hookworm infection showed significantly low serum levels of vitamin B_{12}, as compared with the healthy laboratory workers. Eight of the 21 patients studied showed values of serum vitamin B_{12} below 100 micromicrograms per 100 cc. Twelve of 13 patients with severe hookworm infection showed impairment of the pteroylglutamic acid intestinal absorption; however, none of them showed megaloblastic proliferation in the bone marrow. They all recovered with iron therapy alone. The 5 patients with light hookworm infection and the 5 patients with iron-deficiency anemia but without hookworm infection did not show significant differences in the results of the serum vitamin B_{12} and folic acid tests from those of the healthy persons studied. Although the reported data on vitamin B_{12} and folic acid metabolism are not sufficient to permit a firm conclusion, they nevertheless suggest that, in addition to the blood loss associated with hookworm infection, some other nutritional factors may be involved in patients with this infection.

NEUROLOGY & PSYCHIATRY

Familial Periodic Paralysis: Report of a Case Resistant to Dextrose and Insulin Provocation. R. F. Chen. A. M. A. Arch. Neurol. 1:475-484 (Nov.) 1959 [Chicago].

Familial periodic paralysis is a disease of unknown etiology characterized by recurrent acute attacks of weakness associated with a fall in serum potassium levels. The author cites literature reports to the effect that acute and/or repeated attacks of paralysis may be brought on by a variety of factors, and that familial periodic paralysis must be distinguished from a variety of acute paralytic syndromes, among which are both hypopotassemic and hyperpotassemic conditions. He presents the detailed history of a 14-year-old boy who presented many characteristic features of familial periodic paralysis. He had a familial history; his mother had attacks of weakness in her arms, and 2 uncles on his mother's side had similar paralytic episodes. The symptoms began at puberty, were severer in cold weather, and were absent during the summer; they occurred frequently at night, were precipitated by heavy meals, could be counteracted by active and passive motion, were accompanied by low potassium levels, and could be terminated by the administration of potassium chloride. Although attacks developed at home with great frequency, this patient exhibited resistance to the provocative effects of the administration of dextrose and insulin in the hospital. It is inferred that this resistance was due to a relatively low sodium intake while on a routine hospital diet. The patient experienced attacks despite potassium prophylaxis, but became asymptomatic after receiving dietary admonitions.

There is evidence that the fall in serum potassium level brings about paralysis by altering muscle-membrane potential. Clinical, histological, and metabolic studies suggest fluid and electrolyte changes, mediated by a hormonal abnormality. Greater frequency of attacks at night supports this view. Periodic paralysis associated with hyperthyroidism seems closely related to classic familial periodic paralysis, and there may be some interplay between thyroid, adrenal, and muscle in this disease.

GYNECOLOGY & OBSTETRICS

Effects of Preoperative Irradiation on Adenocarcinoma of the Uterus. H. E. Schmitz, C. J. Smith and W. C. Fetherston. Am. J. Obst. & Gynec. 78:1048-1059 (Nov.) 1959 [St. Louis].

For many years the authors have combined preoperative irradiation with surgery in the treatment of endometrial carcinoma. They do not seek a middle-of-the-road compromise between a surgical and a nonsurgical approach. They feel that preoperative irradiation is an adjunct to the therapy. They review observations on 280 patients with uterine cancer admitted to the gynecologic service of the Mercy Hospital institute of radiation therapy, Chicago, regardless of extent of disease or previous therapy. For comparative purposes, the cases are divided into a series prior to 1946, which has been previously reported, and a series from 1946 to 1953, inclusive, in which more precise and refined techniques were used. In 71 of the patients treated between 1946 and 1953, the preferred techniques were employed, which begin with the insertion of the Y radium applicator on 3 separate occasions for a dose of 2,000 mg.-hr. per application, or a total dose of intracavitary radiation of 6,000 mg.-hr. These applications are at weekly intervals, with the administration on intervening days of deep x-ray therapy through 2 ports, anterior and posterior, with a 1,000 kv. machine and adequate stripping in the midline to protect bladder and rectum from overdosage. After the third intracavitary application, daily external irradiation is continued until a total dose at the midpelvis of 3,500 to 4,000 r is administered. The actual dose to the endometrial surface from the intracavitary radiation is of the order of 20,000 to 40,000 gamma r.

From 6 to 8 weeks after the completion of this program, abdominal hysterectomy, with a generous cuff of vagina and bilateral salpingo-oophorectomy, is performed. Of the 71 patients treated with preoperative radiation followed by operation, 55 showed no tumor in the surgical specimen—a sterilization rate of 77.4%. Similar studies on specimens in the group prior to 1946 showed a sterilization rate of 57%. The authors believe that, even if tumor persists, the irradiation retards the spread of tumor cells. They suggest that irradiation provides a twofold antineoplastic effect, namely, the specific metabolic inhibiting effect through nucleus injury, and what might be termed a general deterrent effect by raising the host resistance either through a general somatic response to a profound physiological injury or by the increase in body resistance mechanisms through the stimulation of radiant energy.

The over-all 5-year survival rate in the 280 patients was 57.2%. In the first series of 138 patients treated between 1934 and 1945, the 5-year survival was 47.4%. The second group of 142 patients treated from 1946 to 1953, inclusive, showed an over-all 5-year survival rate of 67%. This improvement of 20% in the over-all figures can be attributed to improvements in all phases of therapy, inasmuch as it includes patients treated by all modalities. Of the 142 patients in the present series, 106 were operated on, giving an operability rate of 74.7%. This operability rate is rising among the authors' more recent cases, as well as among other reported series. In the aforementioned group of 71 patients the 5-year survival rate was 81.6%, and further analysis shows that it is possible to salvage 96% of patients so treated.

The Detection and Treatment of Carcinoma of the Uterine Cervix at Its Preinvasive Stage: Observations on 58 Patients. Presse méd. 67:1923-1925 (Nov. 7) 1959 (In French) [Paris].

This study is based on observations made on 58 patients with preinvasive carcinoma of the uterine cervix, who were treated between 1950 and 1958 at the St. Louis, Bichat, and Port Royal hospitals in Paris. The patients' ages ranged from 24 to 63 years, the average age being 38.7 years. None of the patients exhibited any symptoms. In 47 of the 58 patients the cervical lesions were clinically considered benign, and in 11 patients the lesions were clinically suggestive of carcinoma. Study of the patients in this series shows that pregnancy seems to play a certain role in the etiology of carcinoma; only 2 patients were nulliparous, whereas 45 were multiparous. The method of choice for the detection of preinvasive carcinoma is considered to be the Papanicolaou smear technique, to be followed, when indicated, by conization of the cervix and histological examination of the tissue removed. Thirteen of the 58 patients were found to have residual carcinoma in the surgical specimens after conization. The incidence of residual lesions after conization seems to depend on the coning technique itself rather than on the glandular invasion and surface extension or depth of the lesion. When all necessary histological criteria are present for the diagnosis of preinvasive carcinoma, the diagnosis as such must be made, whether or not the patient is pregnant.

Surgery is the treatment of choice for carcinoma of the cervix at its preinvasive stage. The safest procedure is a total hysterectomy, with or without preserving the adnexa. More conservative treatment consists of supravaginal cervical amputation or simply conization, which must be reserved for women who wish to keep their reproductive organs. These latter patients must be closely followed over a long period of time. As a rule, the patient is cured by excision of the lesion, and the consistency of these results should stimulate all efforts of early diagnosis of these lesions.

Two Cases of Supernumerary Ovary and One of Accessory Ovary, With an Analysis of Previously Reported Cases. L. R. Wharton. Am. J. Obst. & Gynec. 78:1101-1119 (Nov.) 1959 [St. Louis].

The author presents the histories of a woman with a supernumerary ovary who came under his observation recently, and of one woman with a supernumerary and of another with an accessory ovary from the records of the Johns Hopkins Hospital, Baltimore. He also reviewed the available records of previously reported cases. In practically all studies of this subject, since the first report by Grohe in 1864, the authors have attempted to classify these anomalies. There has been a general agreement on 3 basic principles: 1. The term "supernumerary ovary" includes those rare cases in which the third ovary is entirely separate from the normally placed ovary and apparently arises from a separate primordium or anlage. 2. The term "accessory ovary" includes those cases in which the excess ovarian tissue is situated near the normally placed ovary, may be connected with it, and seems to have been developed from it, possibly from tissue that was split from the embryonic ovary during its early development. 3. The supernumerary or accessory ovary must contain ovarian follicular tissue. Additional criteria have been added during recent years, but some of these were arbitrary and had no embryologic foundation.

In addition to the 2 cases of his own, the author found 2 other cases of supernumerary ovaries in the literature and 18 reports on accessory ovaries. The distinction between the two is at times uncertain, and there have been differences of opinion concerning classification. The author failed to find a single instance in which the correct diagnosis was even suspected before the operation. In most cases, the operator, after seeing the lesion, thought it was fibrous tissue or a lymph node. In a few cases, the structure was so small that it was concealed by adherent pathological masses. Hence, the only cases of accessory or supernumerary ovary that are ever recognized are those discovered at autopsy or in which disorders develop in the accessory or supernumerary ovaries, such as tumors or cystic changes. The exact incidence of this rare condition in otherwise normal women is impossible to determine.

The literature includes 26 reports by different authors, each recording one or more cases of pelvic or abdominal tumors in women who, in addition, had 2 ovaries. Since these tumors were of types that often arise from the ovary, these authors concluded that these tumors must have arisen from a third ovary, and have reported them as accessory or supernumerary ovaries. The pathological diagnoses of these various tumors included dermoid cyst, simple cyst, papillary cyst, multilocular cyst, cystadenoma, pseudomucinous cyst, chocolate cyst, granulosa-cell tumor or carcinoma, and myosarcoma. The literature contains 4 reports of women who continued to menstruate after a bilateral oophorectomy, and it also records 2 instances in which women conceived after a bilateral oophorectomy. The reports concerning the persistence of uterine function after bilateral oophorectomy are difficult to evaluate. The author is inclined to share the opinion of some that in most instances it was due to an incomplete removal of the ovaries, rather than the presence of supplementary or accessory ovaries.

Amniotic Fluid Embolism and Infection. R. G. Valenzuela, H. C. Soto and G. Z. Castagnini. Obst. y ginec. latino-am. 18:335-346 (July-Aug.) 1959 (In Spanish) [Buenos Aires].

The authors report 5 cases of amniotic fluid embolism which occurred among 37,000 deliveries observed on the maternity ward of San Francisco de Borja Hospital in Santiago de Chile from 1956 to 1958. In 2 patients fetal death had preceded labor; in 1 the fetus died soon after labor induction; these 3 patients died before completion of labor. In 2 patients the children were delivered live. In all 5 patients there were signs of amniotic fluid infection manifested by high temperature, chills, and foul odor of the fluid. Only one patient survived, a 35-year old primipara who entered the maternity ward in labor, with weak contractions. After a 48-hour-long uterine inertia, oxytocin was administered intramuscularly, which caused rather intense uterine contractions. The delivery was terminated by cesarean section. During the operation a marked infection was detected, its main sign being the foul odor of the amniotic fluid and of the fetus. The patient developed sudden and intense cyanosis and dyspnea, and excreted a frothy pinkish sputum. Collapse and hypotension with tachycardia occurred. Therapy with lanatoside C, morphine, and oxygen was instituted. A roentgenogram taken the following day showed extensive shadows over both pulmonary fields. At physical examination, a crepitation could be heard. The clinical picture gradually improved, and the roentgenographic image and the fibrinogen level became normal.

The authors believe that the 2 main factors in the causation of amniotic fluid embolism are uterine contractions of a tetanic type and infection. Pulmonary roentgenograms and determination of circulating fibrinogen are valuable aids in the diagnosis. As prophylactic measures, the authors recommend investigation and treatment of infection of the fetus, and advocate restriction and, in some cases, avoidance of oxytocics, especially by the intravenous route. As therapeutic measures, they advise intense oxygen therapy and the administration of opiates and/or artificial hibernation in order to minimize the vagal reflexes produced by pulmonary emboli.

Post-Partum Panhypopituitarism. B. J. Pascoe and A. E. McGuinness. M. J. Australia 2:635-640 (Oct. 31) 1959 [Sydney].

The 8 cases of postpartum panhypopituitarism presented were seen at Sydney Hospital during the last 4 years. The authors call attention to Sheehan's contributions to the understanding of the etiology, pathology, and clinical manifestations of this condition. The 8 cases are divided into 2 groups: (1) 6 cases in which the syndrome remained unrecognized for some years and (2) 2 cases in which the condition was recognized 2 months and 8 days, respectively, after the delivery causing onset of the syndrome.

Tabulations of the data on the first 6 women show that they ranged in age from 35 to 68 years, and that their symptoms had persisted for from 7 to 27 years. With minor variations, these 6 women had the characteristic clinical pattern emphasized by Sheehan, namely, the history of collapse at delivery, followed by absence of lactation and of menstruation; a gradual loss of pubic and axillary hair, pallor, and dryness of the skin; loss of energy, apathy, and mental slowing; disinclination to carry out minor household duties; and abnormal sensitivity to cold. The appearance may be typically myxedematous, or may be that of premature senility. These persons, as a group, are loath to seek medical advice, and if they do so, it is not uncommon for a diagnosis such as anemia or myxedema to be made, with subsequent poor response to therapy. Some patients are admitted to hospital in coma. Laboratory investigations reveal low basal metabolic rates and low urinary steroid levels. There may be anemia, achlorhydria, low blood sugar levels, and a flat dextrose tolerance curve. The corticotropin (ACTH) stimulation test may distinguish the primary hypoadrenalism of Addison's disease from the secondary form occurring in panhypopituitarism. Patients with panhypopituitarism show little or no response on the first or second day of ACTH infusion, but respond significantly by the third day. Thus, they may be distinguished from nonendocrine cases (which respond on the first day) and from cases of primary adrenal insufficiency, which never respond to ACTH stimulation. The history of recurrent pyelonephritis in 3 of the 6 cases may be significant. Mild hypertension was noted in 3 of the women, but this did not seem to be related to renal disease. Pigmentation of the hands, arms, and face was observed in one of the patients. Two patients experienced episodes of coma.

Of the 2 women in whom the panhypopituitarism was recognized early, one was 26 years old. The delivery of her first child had been complicated by toxemia, dystocia, forceps delivery, retained placenta, severe postpartum hemorrhage, and profound shock, requiring transfusion of 3 liters of blood. After recovery, she suffered puerperal infection with pyrexia and offensive lochia. On returning home, she was listless, weak, and apathetic. On the basis of a diagnosis of postpartum panhypopituitarism, she was given 12.5 mg. of cortisone 3 times a day, and 32 mg. of thyroid once a day. This produced great improvement. Six months later she was bright and active, but there was no return of menstruation or of pubic hair. The second patient, a 34-year-old woman, was delivered of a stillborn fetus, with subsequent severe hemorrhage and shock. She died 10 days later, and autopsy revealed complete necrosis of the anterior pituitary lobe. Observations on this series of cases show that the diagnosis of postpartum panhypopituitarism depends on familiarity with its common manifestations and on awareness of its possible occurrence, in varying degrees of severity, as a sequal to obstetric collapse.

Trophoblast in the Circulating Blood During Pregnancy. G. W. Douglas, L. Thomas, M. Carr and others. Am. J. Obst. & Gynec. 78:960-973 (Nov.) 1959 [St. Louis].

It has been established that trophoblast finds its way into the pulmonary circulation of women who die during pregnancy, particularly in circumstances involving convulsions and intrauterine manipulation; terminal events may be responsible for these trophoblastic embolisms. The growth of trophoblast away from villous attachments and its migration into the blood stream may also occur as a normal pattern of behavior, in the same manner as syncytiotrophoblast wanders among the interstices of uterine muscle. One consequence of such migration should be the appearance of trophoblast not only in the lungs but in the circulating blood during pregnancy.

In searching for trophoblast in the circulating blood, the authors employed a method similar to that employed by Moore in the search for cancer cells. They were able to demonstrate syncytiotrophoblast in the circulating blood of pregnant women from the 18th week of gestation to term. The demonstration of syncytiotrophoblast in circulating blood drawn from vessels draining the uterus, at various stages of gestation, makes it clear that the process of deportation may be regarded as a constant migration of this tissue into the blood stream during pregnancy. While the methods employed at the present do not permit an estimation in quantitative terms of the amount of tissue involved or of its relation to various complications of pregnancy, there is no doubt that this phenomenon is an accompaniment of normal pregnancy and not a result of death throes and intrauterine manipulation.

The migration of these cells into the blood stream may be of profound significance. In a broad sense, pregnancy plays the biological role of a homograft, since both placental and fetal tissues have a genetic derivation different from the tissues of the maternal host. The genetic and immunological requirements for successful homotransplantation of tissues are such that grafting between humans has generally been possible only in the case of monozygotic twins. It is clear that in pregnancy some fundamental means have been developed to escape the fate of the homograft, so that existence of the conceptus for the period of gestation becomes immunologically possible. Explanations for this apparent exception to homograft behavior are considered. It may be that the fetal tissue which lies in juxtaposition to maternal tissues, the syncytiotrophoblast, is so embryonal and devoid of antigenic capacity that it is not recognized by the maternal host as an intruder. Or, if the syncytiotrophoblast is recognized as foreign tissue, the mechanisms of rejection are held in abeyance by some intrinsic feature of pregnancy which allows a sort of immunological truce. Production or localization of cortisone or similar steroids by the placenta might also provide for this mechanism of tolerance. A third possibility is suggested by the work of Billingham, Brent, and Medawar, in which tolerance to homografts was induced in animals by the prior injection of the donor's cells. It is conceivable that a similar mechanism is present in human pregnancy, and that the migration of trophoblast into the blood stream throughout gestation is the means by which "tolerance" is achieved.

Abruptio Placentae and Rupture of the Marginal Sinus of the Placenta: Some Relationships. J. H. Ferguson and R. L. Hatton. Am. J. Obst. & Gynec. 78:947-959 (Nov.) 1959 [St. Louis].

The authors explain similarities and differences between abruptio placentae and rupture of the marginal sinus of the placenta on the basis of observations on women with these accidents observed over a 3½-year period at the University of Miami-Jackson Memorial Hospital, Miami, Fla. There were 113 cases of abruptio placentae and 130 cases of rupture of the marginal sinus. All 113 cases diagnosed as abruptio placentae showed changes on the maternal aspect of the placenta that were considered characteristic of this lesion. The placenta exhibited one or more of the following signs: a sizable clot attached to the maternal surface, a depression obviously caused by a clot, or unequivocal changes in the color and texture of the maternal surface. In all 130 cases of rupture of the marginal sinus the placentas satisfied the anatomic criteria for the diagnosis. An attendant at delivery noted that there was a clot at the margin of the placenta and that that clot was continuous with clotted blood in the marginal sinus. If examination of the placenta indicated that the clot had ever been between the maternal surface of the placenta and the uterus, the diagnosis of abruptio placentae was made. The diagnosis of placenta previa was eliminated by vaginal examination.

There were no great differences between the 2 forms of placental accidents with regard to vaginal bleeding or the delivery of premature infants. Vaginal bleeding was observed in 82% of the 113 women with abruptio placentae and in all of the 130 with rupture of the marginal sinus. Premature delivery occurred in 50% of the 111 single births to the women with abruptio placentae and in 46% of the women with rupture of the marginal sinus. In this last group the neonatal mortality rate was high; while 54 of 58 premature infants were born alive, 19 died during the neonatal period. The chief dissimilarity between abruptio placentae and rupture of the marginal sinus is in their danger to the mother and fetus. Abruptio placentae carries grave risks for both mother and fetus, while rupture of the marginal sinus poses less of a threat. It is understandable that true abruptio placentae, with its dissolution of the placenta-uterine union and its shock, should have a high stillbirth rate. Despite a readiness to perform cesarean section, the authors had a 55% stillbirth rate; fetal heart tones could not be heard on admission to the hosptial in 43% of these cases. The stillbirth rate among women with rupture of the marginal sinus was only 2%.

Because of differences in the symptoms of the 2 conditions, the authors were often able to differentiate them before delivery. Seventy-six per cent of the patients with abruptio placentae had one of its typical symptoms, and 32% had the complete triad of pain, hypertonicity, and tenderness of the uterus. These symptoms were rarely noted in cases of rupture of the marginal sinus, and then generally were milder. There were 2 characteristics that abruptio placentae and rupture of the marginal sinus frequently had in common, namely, a tendency for the lesions to occur at the dependent portions of the placenta and a tendency to low implantation. This anatomic similarity suggests that under certain conditions one syndrome may be a precursor of the other.

Spontaneous Rupture of the Liver in a Patient with Acute Toxemia of Pregnancy. D. Retikas and N. Karanouh. Ohio M. J. 55:1523-1525 (Nov.) 1959 [Columbus].

Spontaneous rupture of the liver is rare, only 15 cases having been reported. The 16th case, presented in this paper, was that of a 37-year-old woman, in the 32nd week of her 4th pregnancy, who was admitted to Mercy Hospital, Canton, Ohio, on Sept. 9, 1957, with complaints of headache, dizziness, nausea, and vomiting, associated with slight pain and tenderness of the epigastrium and the right upper quadrant. Her blood pressure was 230/120, and the pulse rate 92 per minute. The uterus was enlarged to the size of a 32-week gestation. The fundus was 3 fingers below the xiphoid process. The patient was admitted to the delivery room with a diagnosis of acute toxemia and possible chololithiasis. Half an hour later, she complained of pain in the epigastrium; the blood pressure dropped suddenly, and 15 minutes later it was unobtainable. The patient appeared to be in deep shock. The fetal heart rate was absent, but the contractions of the uterus became stronger and more frequent. With a diagnosis of abruptio placentae or internal hemorrhage from rupture of the uterus, cesarian section was performed, and a stillborn female infant was extracted.

The woman's abdominal cavity was filled with fresh blood. There was a large transverse laceration, about 6 cm. in length, on the anterior surface of the left lobe of the liver. The anterolateral surface of the right lobe was covered with a subcapsular hematoma. The laceration was packed and sutured. About 15 minutes after surgery, the blood pressure dropped again to zero. During the next five hours the patient was in shock. She died 10 hours after admission. Autopsy was performed, and the following causes of death were assumed: (1) acute focal necrosis of the liver with subcapsular hemorrhage and rupture of Glisson's capsule; (2) intraperitoneal hemorrhage with shock; (3) clinically acute toxemia of pregnancy.

Spontaneous hemorrhage of the liver may result from acute toxemia, but rupture of Glisson's capsule from massive hemorrhage is one of the rarest complications. The patient did not have any marked trauma or convulsion. However, the question of insignificant trauma during the transportation of the patient, as well as during palpation or examination, cannot be ruled out. Toxemic patients are notorious for their tendency to spontaneous hemorrhage, and besides the common hemorrhagic lesions of the liver and the high incidence of premature separation of the placenta, many suffer hemorrhage into the subarachnoid space, into the brain, into the rectus muscle, and into the retroperitoneum from the pancreas. The pathological physiology of eclampsia suggests the importance of fibrinogen depletion as the cause of these hemorrhagic phenomena. Patients in acute toxemia, with pain in the right upper quadrant and the epigastrium and with rapid development of shock, should suggest the possibility of rupture of the liver. The only hope for recovery lies in surgery. Measures for hemostasis are suture of the damaged portion of the liver; packing of the laceration with Oxycel, fat, muscle, or omentum; and electrocoagulation by cautery. In severe cases the mortality may reach 50% despite surgery.

PEDIATRICS

Symptomatic Neonatal Hypoglycemia Associated with Toxemia of Pregnancy. M. Cornblath, G. B. Odell and E. Y. Levin. J. Pediat. 55:545-562 (Nov.) 1959 [St. Louis].

This report describes 8 cases of spontaneous hypoglycemia, with signs beginning on the second or the third day of life in infants born to mothers with preeclampsia. Convulsions, apnea, tremor, and limpness in these infants were immediately alleviated after parenteral administration of dextrose, which sometimes had to be maintained for prolonged periods in order to keep the blood sugar at normal levels. The age at onset of these signs varied between 40 and 72 hours. Six of the 8 infants were considered premature, at least by weight (in 7 cases the length of pregnancy was 36½ weeks or longer). All had been fairly well until the onset of the first signs of hypoglycemia, which were listlessness and refusal of feeding after having taken milk well. These signs were followed by loss of muscle tonus and, after a variable period of time, by cyanosis, tremors, and convulsions. The blood sugar level at the time of the convulsions ranged between 1 and 24 mg. per cubic centimeter. In 5 infants the spinal fluid sugar ranged from 0 to 15 mg. per cubic centimeter. Various tolerance tests were performed in an attempt to elucidate the etiology of the hypoglycemia observed. These included administration of glucagon or epinephrine, as a test for available hepatic glycogen, and of casein or leucine, as a test for hypoglycemia precipitated by amino acids.

Five of the infants reported were well at the time of the follow-up study, made within 44 days to 11 months after birth. Two infants suffered permanent damage of the central nervous system, and one died at the age of 17 days. The occurrence of hypoglycemia in these 8 infants suggests that this condition plays a role in the high morbidity and mortality rates among children born to mothers with preeclampsia. The high rates may be due, in part, to the administration of drugs, such as barbiturates, morphine, and the hexamethonium compounds, to the mother, but for the most part the cause of the disease is unknown. Since hypoglycemia can be responsible for apnea, cyanosis, limpness, and convulsion in the newborn infant, it should be considered in the differential diagnosis in the offspring of toxemic women. The need for more careful observation of these infants in the nursery is apparent.

A Note on the Development of Gaucher Cells in a Newborn Infant. J. Bernstein and W. E. Shelden. J. Pediat. 55:577-581 (Nov.) 1959 [St. Louis].

This report describes the uncommon occurrence of signs and hematological abnormalities characteristic of Gaucher's disease in a newborn infant. Although the "storage" cells were cytologically atypical, this development provided an opportunity for observing the cellular changes in the earliest stages of the disease. The infant, a girl weighing 6 lb. 5½ oz. (2,876 Gm.) at birth, was born after a normal full-term pregnancy. The parents were apparently healthy, although the father later died of carcinoma of the pancreas. Of 2 other children, one was normal and the other, a 3-year-old, had suffered from chronic Gaucher's disease for 1½ years. Besides exhibiting signs of Mongolism and cutaneous purpura, the infant developed vomiting and diarrhea at 3 days of age. She was then transferred to the Children's Hospital of Michigan, in Detroit. The blood cell count per cubic millimeter was 6.5 million erythrocytes, 18,150 leukocytes (on admission to the hospital; 7,000, 4 days later), and 38,250 platelets (falling to 13,400). Despite negative stool cultures, the infant continued to suffer from diarrhea and episodes of cyanosis. Her condition progressively deteriorated, and she died after a severe cyanotic episode, at the age of 14 days.

At autopsy, large abnormal cells were found in the spleen, containing fibrillary cytoplasm which could be stained with the periodic acid-Schiff, Sudan black B, and Hale dialyzed iron procedures. Only the spleen was increased in size. The liver and bone marrow contained scattered, large, lightly Schiff-positive cells resembling those in the spleen. The only abnormality in the brain were nerve cell heterotopia in the white matter and cerebellar cortical disruption, of the type frequently found in Mongolism. Normal levels of glycolipids were found in the spleen and liver, which suggest that in Gaucher's disease the abnormal cells make their appearance before the storage of glycolipids takes place. For purposes of classification, this case should be considered as an example of the chronic form of Gaucher's disease in a very young child, in whom thrombocytopenia (usually a late hematological manifestation) appeared within a few days after birth.

Strongyloidiasis. P. Huchton and R. Horn. J. Pediat. 55:602-608 (Nov.) 1959 [St. Louis].

Sixteen patients with strongyloidiasis have been observed at the Vanderbilt University Hospital, Nashville, Tenn., since 1938; 7 were adults and 9 were children, between the ages of 16 months and 8 years. The most constant laboratory finding in this series was eosinophilia, present in 13 patients. Anemia was detected in 11 patients; leukocytosis, in 10; occult melena, in 5; and hypoproteinemia, in 5. The most frequent clinical signs and symptoms were diarrhea, vomiting, and weight loss which were present in 9 patients. Weakness was observed in 8 patients; abdominal pain, in 7; and anorexia, fever, or a semistuporous state, in 5. Edema, melena, urticaria, cough, and dyspnea also appeared in several patients. Constipation, nausea, indigestion, malaise, and headache were less frequent symptoms. The initial clinical impression given by these patients was parasitic infection in 5, nephrotic syndrome in 3, and malnutrition in 4. Acrodynia, celiac syndrome, multivitamin deficiency, pneumonia, and penicillin reaction were listed one time each in a differential diagnosis. In 15 patients the larval forms were found in stool specimens. In the 16th the diagnosis was made at autopsy. Eleven patients were treated with methylrosaniline chloride (gentian violet) only; 3 received diethylcarbamazine citrate (Hetrazan); and 1 received dithiazinine iodide (Delvex); one patient received no treatment. One patient was cured; another was presumed to be cured; 2 were known to be still infected at the time of follow-up; and 4 were presumed to be still infected. Five patients could not be contacted; and 3 children, between the ages of 16 months and 3½ years, died.

The main finding at autopsy in the children who died was infection with Strongyloides stercoralis in the intestinal tract; pulmonary hemorrhage was observed in all 3 children, and duodenal and jejunal ulcers were found in 2. The authors call attention to the potential seriousness of this disease and to its pathogenesis. Prophylaxis of strongyloidiasis is based on the proper disposal of feces, wearing of shoes, and avoidance of contact with soil known to be contaminated. The therapeutic problem has not yet been solved. The newest and most promising anthelmintic is dithiazinine, which must be administered orally since it is damaging to the renal tubules if given parenterally.

Epidemiologic, Clinical, and Laboratory Features of an Epidemic of Type 9 ECHO Virus Meningitis. P. Solomon, L. Weinstein, Ten-Wen Chang and others. J. Pediat. 55:609-619 (Nov.) 1959 [St. Louis].

A group of 64 patients (56 children and 8 adults) was studied at the New England Medical Center during an outbreak of aseptic meningitis, with a significant incidence of skin eruption, which occurred in the Boston area in the summer of 1958. Forty-five patients were males, and 19 females, which confirms the predominance of the disease among males. The great majority of the patients in this series were under 10 years of age, with the highest incidence in the 7-to-8-year age group. The onset of signs and symptoms dated from 3 weeks to less than one day prior to admission to hospital. In 11 patients there was a biphasic course, with the initial illness lasting for a few days, followed by an asymptomatic period, and then by recurrence of the symptoms. The maximal rectal temperature recorded varied between 99.8 and 105.6 F (37.5 and 41 C). Only one patient was afebrile during the entire duration of the disease. All the patients who were able to report on their symptoms complained of headache. Nausea or vomiting or both occurred in 46 (80%) of the 56 patients under 20 years of age, and in 3 of the 8 adults; abdominal pain was present in the children only. Skin eruption was noted in 18 patients (28%), of whom only 1 was over 10 years. Symptoms of respiratory infection were not prominent. Cough, coryza, and sore throat were present, respectively, in 16, 7, and 9% of the patients, with only one adult complaining of coryza. Nuchal rigidity was present in only 11% of the patients. Four patients had manifestations of more extensive involvement of the central nervous system; one had hallucinations, 2 were "talking nonsense," and one (1-year-old) had a generalized seizure with a sudden rise in temperature. The last 3 patients had proved infection due to enteric cytopathogenic human orphan (ECHO) virus, type 9.

Stools and spinal fluid were obtained from the patients soon after their hospitalization. Prepared stool suspensions and spinal fluids were stored at —20 C until inoculation into tissue culture. Acute and convalescent serums were collected at an interval of at least one week. Primary cell cultures of human amnion and Rhesus monkey kidney were used for isolation and identification of the virus, but only the latter was used for the neutralization tests. Titration of the neutralizing antibodies in the serum was also carried out in monkey kidney tissue culture. ECHO virus, type 9, was proved to be the etiological agent in 45 (70%) of the patients studied, by isolation of the virus from the spinal fluid or by demonstration of a fourfold increase in the neutralizing antibody titer or by both. In 5 other patients (8%) ECHO virus was considered the causative agent, despite failure to isolate it from the spinal fluid and despite the absence of a significant rise in antibody. ECHO virus, type 9, was not implicated in only 2 instances in which complete investigation was possible. In 14 patients (22%) no etiological agent could be demonstrated; in 12 of these it had not been possible to obtain adequate material for virologic or serologic studies. This fact, plus the inability to demonstrate other viral agents, and the marked similarity between the clinical pictures observed in this series and those found in previous outbreaks justify the conclusion that the etiological agent in the great majority, if not all, of the 64 patients studied was ECHO virus, type 9.

Congenital Neurocutaneous Syndromes of Childhood: III. Sturge-Weber Disease. D. H. C. Chao. J. Pediat. 55:635-649 (Nov.) 1959 [St. Louis].

Nine patients with nevoid amentia (Sturge-Weber disease) were observed at the Blue Bird Circle children's clinic of the Methodist Hospital in Houston, Texas. Their ages, when first seen, ranged from 7 months to 7 years; the age at onset of the symptoms varied from 2 to 7 months, with the exception of one child in whom the onset occurred at 3 years. The basic angiomatous malformation of Sturge-Weber disease was observed in all 9 patients. All of them presented facial nevus. Neurological findings were hemiparesis in 6 children, atrophy in 5, and increased knee jerk in 1. There was left-sided ocular involvement in all the patients with the exception of one who was born with bilateral buphthalmos. This patient, a 7-year-old boy, received a diagnosis of atypical Sturge-Weber disease because of 3 features in his clinical picture: 1. The distribution of the facial nevus did not follow that of the sensory branches of the trigeminal nerve. 2. The angiomatous malformation was an arteriovenous angioma. 3. Extensive cutaneous lesions, repeated episodes of gastrointestinal hemorrhage, and the fact that the father had telangiectatic lesions suggested that the vascular anomaly might be widespread. The author considers this clinical picture as representing a "variant" of Sturge-Weber disease, and points out the possibility of a transitional hybrid form between the Sturge-Weber and the Osler disease. This child was also the only one in the series to be free from seizures.

Of the 7 children who were of school age when this study was made, only 2 were attending regular classes (including the patient with atypical Sturge-Weber disease). One, who had an IQ of 60-70, was attending a special class; the others were mentally incapable of school work. Three of them were unaware of their surroundings, 2 never developed speech, and 1 could say only one word. Two patients underwent a brain operation, by hemispherectomy in one and by block resection of cerebral lesion in the other. In both patients the seizures disappeared. Two of the 4 patients with glaucoma were operated on for relief from the intramuscular tension. One patient responded well to Diamox therapy, which in this instance served both as an anticonvulsant and as an antiglaucomatous agent. It is the author's opinion that early surgical extirpation of unilateral lesions may prevent functional deterioration as well as bring symptomatic relief from seizures.

Anabolic, Liver-Protective and Antianemic Action of a Combined Treatment with Liver Extract and High Doses of Vitamin B_{12} in Pediatrics. L. Francalancia and R. Cremoncini. Minerva pediat. 11: 944-954 (Sept. 22) 1959 (In Italian) [Turin, Italy].

A treatment with liver extract, combined with high doses of vitamin B_{12}, was given to 6 groups of children with various conditions; the combined dose consisted of 4 units of liver extract and of 0.5 mg. of vitamin B_{12}. The duration of the treatment ranged from 5 to 30 days, and the drugs were administered intramuscularly twice a day, once a day, or every other day. Gain in body weight and marked increase in both hemoglobin and globulin levels, accompanied by improved vitality, appetite, and euphoria, were the results of the treatment in 10 infants, aged between 3 and 11 months, with hypochromic anemia. The treatment resulted in gain in body weight, increase of serum hemoglobin level and of red blood cells, normalization of the Katz formula and of total proteinemia value, disappearance of asthenia and anorexia, as well as regained color of the skin and of visible mucosae in 15 children, aged from 2 to 9 years, who were convalescing from parotitis, measles, smallpox, scarlet fever, paratyphoid, or infectious mononucleosis. The treatment removed acetone-like breath, ketonuria, and vomiting in 8 children, aged from 3 to 6 years. It brought about normalization of hepatic function and improvement in the general state in 4 children, aged between 5 and 7 years, who were convalescing from a severe form of infectious hepatitis. Normalization of the hepatic function and of protein and lipoprotein values, demonstrated by electrophoresis, was obtained in 5 children with tuberculosis. Regained body weight, appetite, and vitality, with improvement in red blood cell count and in hemoglobin and globulin levels, resulted in 7 children with trophic failure. The combined therapy with liver extract and vitamin B_{12} thus produced an efficacious synergic action in these patients.

UROLOGY

Vesico-Ureteral Reflux in Children: Diagnosis and Management. V. A. Politano. J. South Carolina M. A. 55:417-421 (Nov.) 1959 [Florence].

A critical review of the literature indicates that roughly 10 to 12% of children presenting urologic complaints will demonstrate vesicoureteral reflux. Every child with repeated urinary tract infections, residual urine, unexplained fevers, vague abdominal complaints, or flank pain should be studied by cystography. This valuable diagnostic procedure should not be eliminated when intravenous pyelograms have been reported as normal. This condition, if allowed to go untreated, will eventually lead to total renal destruction, either from progressively increasing back pressure or from repeated infections. Neurogenic disorders should be corrected with appropriate drug therapy or surgical modification of the neurological deficit when possible. Residual urine secondary to vesical neck obstruction must be eliminated by catheter drainage, multiple voidings, urethral dilatations, or transurethral or open resection of the vesical neck or other obstructing lesion. Every conservative effort to eliminate reflux should be attempted first. If these measures fail, reimplantation of the ureters by a submucosal tunnel is necessary. The author reports the history of 3 children, aged 4, 6, and 12 years, in whom vesicoureteral reflux was successfully corrected by the creation of a submucosal tunnel.

Results of Treatment of Carcinoma of the Prostate with Diethylstilbestrol Diphosphate (Honvan). H. G. Kletschke. Ztschr. Urol. 52:615-622 (Oct.) 1959 (In German) [Leipzig, Germany].

The author reports on 106 men with carcinoma of the prostate, who were treated with diethylstilbestrol diphosphate (Honvan) in the urologic department of a Berlin hospital between 1953 and 1957. This method of treatment was indicated by metastases in 68 patients, increased serum acid or alkali phosphatase level in 49, renal congestion due to walling in of the ureteral ostiums by the carcinoma in 8, age of less than 60 years in 12, and resistance to estrogen therapy in 38. The patients were given intravenous injections of 2 ampuls (500 mg.) of the drug daily, followed by oral maintenance therapy in 15 patients. Follow-up examinations in the course of 5 years have shown that treatment with diethylstilbestrol is superior to that with estrogens. In 28 (73.8%) of the 38 patients with resistance to estrogen therapy, a favorable response to diethylstilbestrol was revealed by restoration of the acid and alkali phosphatase level to normal in 6, reduced acid and alkali phosphatase level in 4, improved general condition (increase in body weight) in 10, disappearance of pain in 1, and reduced size of the prostate in 7. Microscopic examination of prostatic tissue was performed in 5 patients before and after treatment with diethylstilbestrol alone, and revealed a favorable effect of the drug on the carcinoma tissue. Regression of bone metastases did not occur, but a definite reduction in the size of the soft tissue metastases was observed.

In 10 patients (9.4%) treatment had to be discontinued because of intolerance (continued nausea). Gynecomastia was observed in only 10 patients (9.4%). Fourteen patients (36.8%) died, and in 4 of these administration of diethylstilbestrol had been discontinued because of intolerance. Diethylstilbestrol is a highly effective drug in carcinoma of the prostate. Although a cure of the carcinoma is not possible, the inhibition of growth of the tumor is greater than that obtained with female sex hormone therapy.

Experiences with Diethylstilbestrol Diphosphate (Honvan) Therapy for Cancer of the Prostate. H. Warlitz. Ztschr. Urol. 52:622-629 (Oct.) 1959 (In German) [Leipzig, Germany].

The author reports on 70 men, of the average age of 77 years, with carcinoma of the prostate who were treated with diethylstilbestrol diphosphate (Honvan) in the city hospital of Neumünster/Holstein, Germany, between 1952 and 1959. The following treatment schedule proved satisfactory. An initial course of 8,500 mg. of diethylstilbestrol was given by the intravenous route, with 500 mg. daily for 10 days and 250 mg. daily for an additional 14 days. When local and general findings, roentgenologic examination, and determination of phosphatase values did not show significant improvement, a second course of 8,500 mg. of the drug was given by the intravenous route. It was possible to increase the daily dose to 1,000 or 1,500 mg., provided that the drug was administered in isotonic sodium chloride solution by intravenous drip. After that, maintenance treatment was practiced with oral administration of 1 to 6 tablets of diethylstilbestrol daily.

The results obtained with this schedule justify the statement that diethylstilbestrol diphosphate is a drug which makes properly directed cytostatic treatment possible. Provided that treatment is instituted early, it is possible for the condition of the patients to be maintained in a state in which they are able to work and are free of complaints. Of the 10 patients in whom treatment was instituted in 1952, one is still living. A 5-year cure was obtained in 5 additional patients in whom treatment was started in 1953-1954. Patients with extensive metastases became free of complaints after a short duration of therapy and were able to work. Several of these patients have been treated successfully for more than 2 or 3 years. Although complete disappearance of bone metastases was not observed, sclerosing phenomena in the area of the bone metastases, associated with corresponding changes in the serum alkali phosphatase level, were observed, which may be interpreted as onset of healing. Complete regression of lung metastasis in the course of therapy was observed in one patient. Maximum daily doses of 1,500 mg. were well tolerated, when administered in isotonic sodium chloride solution by intravenous drip.

Therapy must be continued indefinitely, with 1 or 2 tablets given orally daily to patients without metastases, and with 2 tablets given 3 times daily to patients with metastases. Depending on the results of control examinations and determinations of phosphatase values, the maintenance dose must be determined individually. It should be emphasized that normal phosphatase values—even in patients who do not have any complaints—can be deceptive. In 20 to 25% of the patients with metastasizing carcinoma of the prostate, the phosphatase values were normal. Roentgenologic examinations at certain intervals are, therefore, indispensable during ambulatory after-treatment. The cause of the unreliable results of the phosphatase test has not been elucidated. One might have to deal with completely immature carcinomas which have lost their capability of phosphatase formation.

Acid Phosphatasemia in Apparently Healthy Subjects and in Patients with Prostatic Adenoma and Cancer. O. N. H. Ramos. Rev. clín. españ. 74:164-171 (Aug. 15) 1959 (In Spanish) [Madrid].

Determination of serum phosphatase activity was performed on 90 men, 25 of whom were apparently healthy; 15 patients had prostatic carcinoma, and 50 had prostatic adenoma. In the patients with prostatic adenoma, the serum phosphatase was determined before and immediately after the operation and on the 10th day of the postoperative period. In those with carcinoma, only one determination was made, because they were being treated with estrogens. All tests were performed on fasting patients. The values of serum phosphatase activity in the 25 healthy subjects varied between 0.02 and 0.30 Bodansky units, which is considered normal. The preoperative values were within normal limits in the 50 patients with prostatic adenoma; these values increased in the immediate postoperative period, falling again to normal limits 10 days after the operation. The range of phosphatase levels went from 0.35 to 10 Bodansky units in 13 of the patients with prostatic carcinoma, and was normal in the remaining 2. This increased activity was in direct proportion to the advancement of the neoplastic process. The presence of acid hyperphosphatasemia in carcinoma of the prostate is explained by the increased cellular karyokinesis, especially in patients with osseous metatases. This determination of a semiologic element in cancer of the prostate permits the establishment of a certain diagnosis of the disease.

THERAPEUTICS

Antibiotic Combinations: A Study of the Combined Activity of Streptomycin and Chloramphenicol. N. A. Hinton and J. H. Orr. Canad. M. A. J. 81:819-827 (Nov. 15) 1959 [Toronto].

The authors report a case of gastroenteritis with septicemia due to a strain of Escherichia coli (serogroup 026) in an infant. Disk sensitivity tests revealed the pathogenic organism to be sensitive to streptomycin and to chloramphenicol, but resistant to all other commonly available agents. Streptomycin was first given to the patient, and considerable improvement was noted over the next 24 hours, although he remained very ill. Tube dilution sensitivity tests were carried out, and the combined activity of streptomycin and chloramphenicol was determined by mixing equal volumes of them at a concentration of 16 times the minimal inhibitory concentration of each and comparing the minimal inhibitory concentration of the drugs alone with the concentration of each in the first inhibitory mixture according to Welch's technique. No interaction was noted between the components tested. Chloramphenicol was then administered in order to decrease the risk of the emergence of a streptomycin-resistant mutant, and this step was associated with rapid deterioration in the clinical condition of the patient, who died 36 hours after the institution of chloramphenicol therapy. Extensive laboratory studies then were carried out on the effect of streptomycin and chloramphenicol on this strain of Esch. coli in an attempt to correlate the results with this instance of probable antagonism.

A wide variety of effects were obtained when streptomycin and chloramphenicol were allowed to act simultaneously on this strain of Esch. coli. The particular effect observed at any one time was profoundly influenced by the nature of the medium, the relative and absolute concentrations of the agents, and the time of observation. Two predominant effects were observed. Combinations at bacteriostatic concentrations were associated with indifference, whereas combinations of chloramphenicol with bactericidal concentrations of streptomycin showed distinct antagonism. The interpretation of these findings, in terms of the treatment of disease in man, is a hazardous undertaking. However, it would seem not unreasonable to hold that, with streptomycin and chloramphenicol or with a similar pair of drugs which gave the same interaction in vitro, if the infection being treated was one in which a bactericidal effect was essential, one might expect to observe evidence of antagonism when the 2 therapeutic agents were used together. In the case of Esch. coli septicemia reported, the bactericidal action of streptomycin may have been essential to survival, and the addition of the interfering agent was largely responsible for the fatal result. A great many infections, however, will respond satisfactorily to treatment with essentially bacteriostatic agents, and in these infections the antagonistic action of chloramphenicol would probably not be observed. Experimental infections were produced in mice with Esch. coli and a Salmonella species, and the effects of combinations of chloramphenicol and streptomycin on these infections were tested. In these animal experiments both indifference and antagonism were shown.

Special Indications and Risks of Cortisone Treatment in Patients with Carcinoma of the Breast. W. Schermuly. Strahlentherapie 110:393-400 (no. 3) 1959 (In German) [Munich, Germany].

In recent years cortisone and its derivatives have been added to the list of hormone preparations recommended for the treatment of patients with carcinoma of the breast. Besides the possibility of permanent therapy with high doses of 50 to 100 mg. of prednisolone or 100 to 200 mg. of hydrocortisone daily for patients whose tumors do not depend on the production of estrogens, or in whom the effect of procedures aimed at the suppression of estrogens, such as castration or androgen therapy, has been exhausted, cortisone and its derivatives, given in small doses of 10 to 20 mg. daily, may play an important part in the management of some emergencies occurring in the course of metastasizing carcinoma of the breast. These emergencies include damage to the bone marrow, cerebral metastases with neurological and psychiatric symptoms, insufficiency of the adrenal cortex, and hypercalcemia.

The author reports on 2 women, aged 56 and 50 years, respectively, with carcinoma of the breast, who were treated with cortisone and prednisolone at the polyclinic of the University in Marburg on the Lahn. In the first of these 2 patients, the characteristic metabolic changes of osteomalacia, namely, hypocalcemia, hyperphosphatemia, hyperphosphatasemia, and low excretion of calcium in the urine, were elicited by the treatment with 10 mg. of prednisolone per day for more than 4 months, combined with a diet poor in calcium. Severe pain in the left femur suggested a pathological fracture of the femur. Healing of the osteomalacic zone of alteration in the bone, with satisfactory loading capacity, resulted from vitamin D therapy and addition of milk to the diet. Before the institution of this therapy the phenosulfonphthalein (phenol red) test revealed a reduced excretion of the dye (22% instead of 40%). Albumin opalescence to clouding was observed in the urine, and also some leukocytes and erythrocytes. Later one macroscopic hematuria occurred, and still later there was discharge of urinary calculi, which was associated with mild pain. The prednisolone therapy mitigated an infection of the urinary passages, but discontinuation of this therapy caused exacerbation of this infection, and the impaired kidney proved very sensitive to the vitamin D therapy. Long duration of hypercalcuria and formation of urinary stones are predisposing factors. In the second patient who had bone metastases, prednisolone therapy with daily doses of 5 mg. of the drug, combined with a low-calcium diet, elicited within 3 weeks hypocalcemia and an excessive increase in alkali phosphatase level, with a typical slow drop to the initial value within 10 weeks.

In addition to the well-known hazards of treatment with cortisone and its derivatives, hypocalcemia and osteomalacia may occur even in patients who are receiving small doses of these drugs, if sufficient amounts of calcium are not administered. Cortisone and its derivatives diminish the absorption of calcium from the intestinal tract and the uptake of calcium phosphate by the bones. Since much calcium is lost by extensive bone metastasis, hypocalcemia and osteomalacia may occur suddenly. There is also the increased possibility of infection of the urinary tract during cortisone therapy.

PATHOLOGY

Effects of High Protein Intakes on Cholesterolemia and Atherogenesis in Growing and Mature Chickens Fed High-Fat, High-Cholesterol Diets. R. Pick, J. Stamler and L. N. Katz. Circulation Res. 7:866-869 (Nov.) 1959 [New York].

The authors report the results of 4 series of experiments carried out on 210 chickens. The first 3 series were performed on growing birds during weeks of age from 12 to 18, 9 to 14, and 13 to 18 respectively. In these experiments all birds were given a mash containing 1% cholesterol and 5 to 10% fat. The experimental birds were given 34 to 50% supplements of protein (soy bean protein, casein, fish protein, liver protein, or egg albumen) added to the mashes. The contrastest birds consumed mash containing 15 to 20% protein. In the 4th series, mature birds were studied when 21 to 30 weeks of age. The birds were divided into 6 groups, all of which consumed mash containing 1% cholesterol and 5% cottonseed oil. In 3 groups (one of roosters, one of intact hens, and one of oviduct-ligated hens), 54% sucrose was added to the mash, reducing protein content to only 8%. In the other 3 groups (one of roosters, one of intact hens, and one of oviduct-ligated hens), the diet contained 20% protein. The results showed that high-protein intake suppresses hypercholesteremia and atherogenesis in young cockerels o[illegible] holesterol, high-fat diets. This happens with supplementation by any nutritionally good protein and is manifest irrespective of source of cholesterol and type of fat. In mature roosters or hens—as in young growing cockerels—low-protein intake intensifies, and adequate protein intake suppresses, hypercholesteremia and atherosclerosis occurring with high-cholesterol, high-fat diets. However, inhibition of coronary atherogenesis induced in hens by endogenous estrogen secretion continues to supervene, despite low-protein intake. Oviduct ligation prevented intensification of hypercholesteremia and atherosclerosis with low-protein intake.

Tumor Cells in the Blood. I. Salgado, J. F. Hopkirk, R. C. Long and others. Canad. M. A. J. 81:619-622 (Oct. 15) 1959 [Toronto].

The blood obtained from 100 patients was studied for circulating tumor cells at the Royal Victoria Hospital and McGill University, Montreal, during 1958 and 1959. Seventy of the patients had various types of cancer, and 30 had noncancerous disease and were used as controls. No abnormal cells were found in these latter 30 patients. Blood was collected from the vein draining the tumor site in 10 patients with cancer, and tumor cells were found in the blood of 4. Blood was drawn from the antecubital vein in 60 patients with cancer, and tumor cells were found in the blood in 57% of the patients. Thirty-two of the patients in whom blood was drawn from the antecubital vein had carcinoma of the breast, and tumor cells were found in the peripheral blood in 53% of the patients. When the cases of carcinoma of the breast were subdivided, certain differences appeared. Tumor cells were found in the peripheral blood in 63% of the 24 patients with carcinoma of the breast in whom blood was drawn within 9 days after radical mastectomy and who were found to have metastases in the axillary lymph nodes, and in 33% of the 15 patients in whom blood was drawn within 9 days after radical mastectomy and in whom the axillary nodes were not involved. Tumor cells, however, were found in only 25% of the 8 patients with carcinoma of the breast with widespread metastases. No tumor cells were found in the peripheral blood obtained before mastectomy in 5 patients with carcinoma of the breast, but were found in the blood drawn 2 hours after mastectomy in 3 of these patients.

The authors emphasize that great caution should be excercised in applying these findings. The presence of tumor cells in the blood does not necessarily mean that metastases will develop in the patient. Only by following up for many years large series of patients in whom blood has been tested for tumor cells can a satisfactory conclusion be reached as to the prognostic significance of tumor cells in the blood.

BOOK REVIEWS

The Care of Minor Hand Injuries. By Adrian E. Flatt, M.A., M.D., F.R.C.S., Assistant Professor of Orthopedic Surgery, State University of Iowa, Iowa City. With foreword by Carroll B. Larson, M.D. Cloth. $9.50. Pp. 266, with 109 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3; Henry Kimpton, 134 Great Portland St., London, W. 1, England, 1959.

There has been a need for a book on injuries of the hand which can be treated properly without admitting the patient to the hospital. Most of the operations described here can be performed safely under local anesthesia. Since the difference between minor and major injuries is artificial, this book has a wider application than the title would imply. The first section outlines the general principles of care, and the second deals with the treatment of specific injuries. The concise text is complemented by photographs of wounds before, during, and after treatment. Details of many operations are clarified by line drawings. A well-selected list of references is included at the end of the book.

Most of the principles and techniques presented can be applied equally well to more severe injuries of the hand. The four chapters on general principles should be read before proceeding to the description of specific injuries. The latter material is arranged conveniently for quick reference. One safe and practical method of handling each problem is described. There are chapters on injuries from mechanical forces and on burns and hand infections. Some injuries and infections included in the text cannot be managed without general anesthesia, and the author clearly indicates those situations. This book can be recommended highly for interns and residents assigned to an emergency surgical service. It should be an invaluable aid to general physicians and industrial surgeons who meet these emergencies daily.

Sexual Impotence in the Male. By Leonard Paul Wershub, M.D., F.A.C.S., F.I.C.S., Associate Professor of Urology, New York Medical College, New York City. With foreword by Ralph E. Snyder, M.D., President and Dean, New York Medical College. Cloth. $5.75. Pp. 126, with 6 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

The author emphasizes the need for appreciation of the problem of sexual impotence in the male by general practitioners, urologists, internists, and others. The causes are ably classified as organic, quasiorganic, and functional (psychic). The author gives a fine summary of the various organic causes, together with corrective measures when indicated. Quasiorganic causes include postprostatic and other surgery of the urinary tract. Post-traumatic impotence is discussed. The author states that in 90% of all cases sexual impotence is functional but that referral to a psychiatrist is unnecessary except for patients with major psychoses. This book is an excellent guide for any physician who encounters patients with sexual impotence.

The Artificial Feeding of Normal Infants. By William Emdin, M.D., D.P.H., Ph.D. Cloth. 16 shillings. Pp. 113. Howard B. Timmins (Pty.) Ltd., 109 Long St., P. O. Box 94, Cape Town, South Africa, n. d.

The first part of this small volume deals briefly with the theoretical composition of artificial milk mixtures. The second part discusses the practical aspects of artificial feeding (calculation of the formula, choice of milk, and feeding schedules through the first year). The third and final section contains chapters on food additives other than milk, including the necessary vitamins, and concludes with specimen diets through the second year. This manual should be a helpful guide for the artificial feeding of normal infants anywhere.

Hypnosis and Related States: Psychoanalytic Studies in Regression. By Merton M. Gill, M.D., and Margaret Brenman, Ph.D., Cloth. $7.50. Pp. 405. International Universities Press, Inc., 227 W. 13th St., New York 11, 1959.

Memory and Hypnotic Age Regression: Developmental Aspects of Cognitive Function Explored Through Hypnosis. By Robert Reiff, Ph.D., Chief Psychologist, Jewish Board of Guardians, New York, and Martin Scheerer, Ph.D., Professor of Psychology, University of Kansas, Lawrence. Cloth. $5. Pp. 253 International Universities Press, Inc., 227 W. 13th St., New York 11, 1959.

These two books have in common the publisher, time of issuance, general subject matter, and special emphasis on hypnotic regression. For this reason they will be reviewed in relation to each other. The statements on their cover jackets are in marked contrast. The second book is described simply and modestly as a carefully made scientific, theoretical, and experimental study based on certain procedures and yielding results of value in developing further research. Such a description should constitute an invitation to read and learn.

The statements describing the first book are of another character. The tripartition of the title into "Hypnosis," "Related States," and "Psychoanayltical Studies in Regression," with the third part as a subtitle, causes doubt as to the major content of the book, in view of the inherent difficulties of coordinating such divergent topics. One must consult the book itself to discover the actual emphasis of meaning in the title. The front inside flap offers a description of the book's content as the psychoanalytical "interpretation of data gained in an extensive research project on hypnosis. They [the authors] re-examine their basic frame of reference, clarify some of its assumptions" and thus "make a genuine contribution not only to the understanding of the variety of hypnotic phenomena but also to the nature of regression." No clarifying statement is suggested as to how all this is done. There is the added statement, "The breadth and scope of this book are evident from the areas which are extensively covered." There follows a 20-item listing. Some of the items are fugues and multiple personalities and hypnosis; brain washing and hypnosis; Balinese trance states and hypnosis; structure of the ego and its subsystems; and five metapsychological points of view in psychoanalysis. Since all this is to be covered in 374 pages, the description tends to imply superficiality and inadequacy.

"Memory and Hypnotic Age Regression," an investigative study of memory by means of hypnotic regression, is written so that it is interesting, stimulating, and informative to the psychologically trained and to the lay reader. The survey of literature is pertinent and comprehensive, and divergent views are carefully appraised and objectively presented. The first three chapters discuss lucidly (1) static and dynamic conceptions of memory, together with environmental and experiential significances, (2) forms and kinds of memory and reconstruction and developmental considerations, and (3) hypnotic age regression in relation to hypermnesia, regressive phenomena, validity of manifestations, and cognitive functioning. Each of these chapters is explanatory and definitive. They clarify the nature of the total study, the available background of scientific studies, and the various divergent conceptual understandings. Of particular interest is the scientific consideration given to psychoanalytical concepts and formulations, something greatly needed and in marked contrast to the adulatory, dogmatic presentation of similar material in the other book.

The fourth chapter is a systematic evaluation, in terms of the possibilities indicated by the past experimental work of others and the thoughts of the authors, of the problems of method, technique, and validity of procedure in presenting tasks, inducing trances, and selecting subjects. The next chapter adequately states the method of investigation in relation to hypotheses, general procedure, and the rationale for the experimental treatment of data. The sixth and seventh chapters present the experiments on emotional and cognitive functioning by a series of ingenious and revealing tests, the experiments on contextual recall by questionnaires, and an appraisal of the validity of experimental findings, including recall of forgotten skills. The results in both types of experimental investigation clearly indicate hypnotic regression to be a valid phenomenon of significant value in the study of memory.

Chapter 8, Methodological Considerations, discusses these experiments in both retrospect and prospect, emphasizing the often overlooked importance of how experimental results are obtained rather than simply their failure or success. The last chapter discusses theoretical considerations in terms of past efforts to theorize and the opportunities offered by the experimental findings reported for new theoretical and experimental approaches to memory and related problems of neurophysiology. The bibliography is well selected and representative, and the book is indexed.

"Hypnosis and Related States" is a disappointing book. It is neither a study of hypnosis, nor a study of related states, nor a psychoanalytic study of regression. It is simply a laborious effort to translate into psychoanalytical terms and theories, by means of simple dogmatic assertions, the authors' various random observations on hypnosis. For example, on page xxiii of the introduction, the following statement appears.

> Our definition of hypnosis is an attempt to integrate the ego-psychological concepts just outlined with the usual view of hypnosis as transference. *The hypnotic state is an induced psychological regression, issuing, in the setting of a particular regressed relationship between two people, in a relatively stable state which includes a subsystem of the ego with various degrees of control of the ego apparatuses.* Obviously this definition is a highly condensed statement, each part of which requires considerable elaboration, a task we undertake in Chapter 5, devoted to the metapsychological theory of hypnosis.

Their own observations of hypnosis, they state, were made incidentally, for the most part, during the long-time therapy of psychiatric patients, on some of whom hypnosis was either attempted or briefly used as an adjuvant therapy. No body of either experimental or observational data is presented. The bibliography, extensively quoted throughout the book, is primarily psychoanalytical in character. The literature on hypnosis, particularly of the last 10 years, has been largely neglected. Examination of the excellent index discloses that posthypnotic suggestion, a major hypnotic phenomenon, is mentioned twice and discussed once in a brief paragraph on page 104. Ego apparatuses, an undefined speculative psychoanalytical concept, receives mention more than 40 times and many paragraphs of discussion.

The Hypnoanalysis of an Anxiety Hysteria. By Fredericka F. Freytag, M.D. Foreword by Milton H. Erickson, M.D. Cloth. $6.50. Pp. 413. Julian Press, Inc., 80 E. 11th St., New York 3, 1959.

During the last 100 years there have been periodic increases in interest in the subject of hypnosis. As a result of the present wave of interest, which began after World War II, numerous articles and books have been published. These publications range from excellent scientific discussions to the Bridey Murphy type of popularization. The present volume is an attempt to record what is called the hypnoanalysis of a single patient. Such reporting s always beset with difficulties, as this volume demonstrates. The technique used seems to be for he most part the induction of a trance state in which the patient believes that he is living in the past. The psychotherapeutic aspects which are osensibly based on psychodynamic principles are questionable. Parts of the book read like a movie cript. The psychotherapy seems to consist of a eries of lectures on psychoanalytic psychology presented to the patient by the therapist. Though he patient is a physician, it is difficult to visualize he value of the various discussions in terms of ego, superego, and other technical phraseology. It hould be noted that Freud, whom the author does not mention, gave up the technique of hypnoanalyis of patients with anxiety hysteria in the 1890's. Of the 22 references, 11 refer to personal communications from one correspondent. Too many books are being written on the subject of hypnosis.

The *Biology of Myelin.* Edited by Saul R. Korey, M.D., Professor of Medicine (Neurology), Albert Einstein College f Medicine, New York. With fifty-one participants. Progress n Neurobiology, volume IV. Series editors: Saul R. Corey, M.D., and John I. Nurnberger, M.D., Chairman and Professor, Department of Psychiatry, Indiana University School of Medicine, Indianapolis. Cloth. $9.50. Pp. 405, with 116 llustrations. Paul B. Hoeber, Inc. (medical book department f Harper & Brothers), 49 E. 33rd St.; New York 16, 1959.

This book comprises 12 papers presented in a ymposium sponsored by the National Institute of Neurological Diseases and Blindness. The authors epresent every field of basic health science as well as related clinical fields. The discussions following he presentations greatly add to the value of the essays. As for all books of this type, a concise review is difficult because the papers are mainly progress reports which the authors do not summarize at the current stage and because there is both dissociation and overlap among them.

For anyone not working primarily in this field t may be a source of amazement that so much can be found in so little. The comparatively inert and uninteresting envelope of the axone has now become a tremendously complex membrane evolving from the plasma membrane of the Schwann cells, or, as Schmitt now proposes, satellite cells. The amellate character of the membrane must exercise great influence on ionic exchange. The nodes of Ranvier are suggested as infoldings of the plasma membranes. Less regular extensions of the membrane into the cytoplasm, often related to accumulations of mitochondria, are also observed. Thus when the essayists speak of the ultrastructure of myelin, it is comparable to the first suggestion of subdividing the atom. Even the single-layered membrane seen in prepared sections for the light microscope is now seen to consist of two layers, each 25 A thick, associated with protein, and separated by a less dense space associated with lipids. Previous polarization and x-ray diffraction studies presaged the suggestion that myelin is a part of the sheath cell and not an axonal secretion. Lamellate organization of protein and lipid occurs also in retinal rods and in chloroplasts.

Nodes of Ranvier are no longer considered as masked naked gaps but are clothed in Schwann cell plasma membranes that condition their vulnerability to ionic influences. The study of mutations has fathered the concept that myelin faults and neurological changes may have genetic origin. When occurring spontaneously in animals, neurological changes are often associated with other abnormalities known or believed to be mutant. Chemical studies of nerve tissue in time relation to myelin formation have been too fragmentary to permit conclusions except that cerebrosides, proteolipids, trypsin-resistant protein, phospholipids, and cholesterol are involved in the process of myelinization. Many study projects are already tied to these observations in relation to age changes in nerve tissue. Wallerian degeneration, axonal regeneration, and experimental encephalitis also received much attention, but definite results reducible to summarization are not yet available.

This is an intensely interesting and valuable series of studies giving promise of specific information in the future. To one who witnessed the skepticism with which early electron microscope studies were received, it is gratifying to see how decisively it has contributed to advances beyond the best that light microscopy could accomplish. The use of illustrations would have been far more helpful to the reader if all types were placed in one numbering system designated by page number instead of the tripartite system used here. Index tables would then be simplified. The growing use of capital letter abbreviations for long complex names, phrases, and technical terms poses a problem for readers not acquainted with the latest, which could be resolved by the inclusion of a glossary briefly explaining each abbreviation.

The Pharmacology and Clinical Usefulness of Carisoprodol. Edited by James G. Miller, M.D., Ph.D., Director, Mental Health Research Institute, University of Michigan, Ann Arbor. Symposium sponsored by Wayne State University College of Medicine and University of Michigan Medical School, Department of Postgraduate Medicine, held in Detroit, Michigan, July 1, 1959. Cloth. Pp. 185, with illustrations. Wayne State University Press, Detroit 2, 1959.

The papers which compose this book deal almost exclusively with reported observations on a new muscle-relaxing, pain-relieving agent called carisoprodol. The pharmacology and clinical studies included cover a wide range of disciplines and observations, including use of the drug in inflammatory and neurological disorders. In general, carisoprodol exhibits some of the properties of its predecessors, mephenesin and meprobamate. The point that the reports are of a preliminary character is emphasized in a summary of the conference that appears with a general index at the end. Some of the papers are followed by references and discussions. These features should increase the value of the book for those who have a particular interest in skeletal muscle relaxants and their use as tranquilizers.

The book achieves its purpose of bringing together, within a single cover, a series of related reports on a new drug. It should be of greatest interest to pharmacological and clinical investigators, chiefly as a pattern for further studies of the subject and related drugs.

Disorders of the Temporomandibular Joint: Diagnosis, Management, Relation to Occlusion of Teeth. By Laszlo Schwartz, D.D.S., Clinical Professor of Dentistry, Columbia University, New York City, and eighteen contributors. Introduction by Charles Ragan, M.D., Professor of Clinical Medicine, Columbia University. Foreword by Harry Sicher, M.D., D.Sc., Professor of Anatomy, Loyola University School of Dentistry, Chicago. Cloth. $15. Pp. 471, with 458 illustrations by Robert J. Demarest. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

This well-documented book was written to be used as a guide for diagnosing and treating disturbances of the temporomandibular joint and its associated structures. It is divided into 37 chapters and is well illustrated. It should be read by anyone who is attempting to diagnose and treat pains in the area of the face and jaw as well as of the temporomandibular joint. It discusses the occlusion of the teeth, the muscles of mastication and their relationship to the temporomandibular joint, and the differential diagnosis of the various causes of pain in the facial area which might be confused with pain in the joint. It covers the methods of treatment, including occlusal grinding, splints, and physical therapy. The diagnosis and treatment of the various disturbances which contribute to pain in the joint, specific diseases and injuries in the joint, and the complications of treatment are also described. An enormous amount of information is included in this volume. Some of the long accepted facts are questioned, and this long overdue book should stimulate more investigation of the temporomandibular joint area.

Cutaneous Manifestations of the Malignant Lymphomas. By Samuel M. Bluefarb, B.S., M.D., F.A.C.P., Associate Professor of Dermatology, Northwestern University Medical School, Chicago. With introduction by Steven O. Schwartz, M.D. Publication number 330, American Lecture Series, monograph in Bannerstone Division of American Lectures in Dermatology. Edited by Arthur C. Curtis, M.D., Chairman, Department of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor. Cloth. $15.50. Pp. 534, with 47 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

Although much remains to be learned about malignant lymphomas, most of what is known may be found in this book. It contains information about mycosis fungoides, Hodgkin's disease, and lymphosarcoma. It includes a short discussion of the immunological status of these related conditions. Etiological considerations, clinical features, symptoms, treatment, and other aspects are described methodically and documented with an unusually extensive bibliography. The author's comments and illustrations are to the point. Individual case histories and the myriad of facts make for slow reading, but the data presented is adequate compensation. Though this source book was written primarily for the dermatologist and other investigators, all persons interested in malignant lymphomas should find it full of useful information.

Metabolic Care of the Surgical Patient. By Francis D. Moore, M.D., Moseley Professor of Surgery, Harvard Medical School, Boston. Cloth. $20. Pp. 1011, with 143 illustrations by Mildred Codding, A.B., M.A., Surgical Artist, Department of Surgery, Harvard Medical School. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

This is a superb new book which covers material not previously available in one volume. It is extremely practical since it discusses problems that are encountered in daily care of the patient, as well as how to search for and combat irregularities. Knowledge in this surgical area has been greatly expanded in the past 15 years. This book, by authorities in the field, is up to date and well organized.

A wide range of subjects, including surgical endocrinology and metabolism, is covered. Important subjects such as normal and abnormal convalescense, hematological findings, fluid and electrolyte management, and repair of tissues and wounds are presented in detail. An outstanding feature is the clear and concise way in which the physiological bases of various conditions are explained. Diseases of the gastrointestinal tract are given special consideration providing ready answers for many problems. The book discusses all processes affecting surgical convalescence, including dehydration, starvation, potassium deficiency, healing, adrenal failure, anemia, and shock. All types of feedings, including tube feedings, are discussed in detail. Case histories are used to illustrate principles of treatment and day-to-day problems. There are sufficient illustrations, charts, and tables to clarify and demonstrate points of interest plus an extensive bibliography at the end of each section. The book is practical and comprehensive and should be of great value to everyone involved in the care of the surgical patient.

QUESTIONS AND ANSWERS

NOCTURNAL ARTHRITIC PAIN

To the Editor:—*I have had rheumatoid arthritis for 28 years and have been taking aspirin in a dosage which is sufficient to alleviate discomfort during the day but does not control the pain during the night. An increase in the dose causes indigestion, and I get no relief from enteric-coated tablets. What medicament should I take?*

M.D., Illinois.

Answer.—There is a recently produced salicylate tablet which is covered with two or three coats of a substance which delays the absorption of the active ingredient of the tablet for several hours. This type of salicylic acid derivative should be tried. Although enteric-coated aspirin may not have been of benefit, the new preparation, which consists of potassium salicylate, 0.30 Gm., ascorbic acid, 0.05 Gm., and potassium para-aminobenzoate 0.3 Gm., made up in tablet form, may be helpful. A small dose of a corticosteroid, such as methylprednisolone, one 2-mg. tablet at 8 or 9 p. m. before retiring, may ease the night pain and stiffness. A suitable sedative, such as pentobarbital, secobarbital sodium, or glutethimide, can be taken as an adjunctive medicament to ease discomfort during the night. Many patients are helped by taking a warm tub bath before retiring.

AIR TRAVEL AND MENSTRUAL IRREGULARITY

To the Editor:—*Has travel by propeller plane or jet aircraft ever been considered a direct etiological factor in menstrual irregularity?*

M.D., Illinois.

Answer.—In over 20 years of association with stewardesses or hostesses on commercial airlines in the United States, I have no evidence that flying in any type of aircraft (propeller, jet propeller, or jet) is an etiological factor in menstrual irregularity. These women are 18 to 30 years old, an age in which a normal amount of menstrual irregularity occurs. If menstrual irregularity occurs at the time they begin work in the airline, we feel that it has no relationship to flying and that it would have occurred had they been working in one of the offices on the ground. During the employee physical examination the degree of dysmenorrhea which a woman may have is ascertained, because she is expected to continue working whether she is menstruating or not to maintain regularly scheduled flights. The Air Transport Association of America has a medical committee which is composed of the medical directors of all the major airlines. This committee has no evidence to date which contradicts this answer to the query.

OPIUM SMOKING

To the Editor:—*A patient with advanced and incurable carcinoma suffers occasional bouts of intense pain. He is unable to retain orally administered narcotics. Hypodermic injections of narcotics for relief from pain are effective but often no person qualified to give these injections is available. Can your consultants suggest whether tinctura opii (USP) is a suitable raw material for opium "smoking"?*

H. H. Neumann, M.D., Elmont, N. Y.

Answer.—No proposal has ever been made in the formulation or application of national or international measures designed to control smoking of opium (or opium preparations suitable for smoking) to permit exceptions because of the alleged medical need for such a use of this substance. Early in the history of our internal revenue laws a prohibitive tax was placed on the manufacture of smoking opium, and our Narcotics Import and Export Act prohibits the possession, receipt, or importation of opium prepared for smoking; it is subject to summary seizure and forfeiture. The laws of the United States, therefore, do not recognize any medical use for smoking opium or opium prepared for smoking.

MIGRAINE HEADACHES

To the Editor:—*Would you have a consultant give an appraisal of desensitization treatment for the prevention of migraine headaches?*

J. B. Eviston, M.D., Huntington, Ind.

Answer.—There is no proof that a patient who has migraine headaches is allergic to histamine, nor has it been established that repeated injections of histamine will desensitize such patients. On the other hand, some physicians have reported fair to good results in patients who have migraine headaches or histaminic cephalalgia. Most allergists believe that the proper therapy for true or typical migraine consists of four steps: (1) discovery of the cause by a carefully taken history, with subsequent elimination of certain foods and deliberate feeding, one at a time, of suspect foods; (2) more or less permanent removal of any foods which seem to cause the migraine; (3) control of any contributory factors, such as emotion (The importance of the emotional factor decreases if the causative food, e. g., milk or pork, is discovered and removed.); and (4) use of ergotamine tartrate for acute attacks. (If the cause is discovered, ergotamine also becomes of secondary importance.)

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INFANTS WITH FLATFOOT

To the Editor:—*I would like to know what treatment for flatfoot should be prescribed for a 15-month-old infant who weighs 27 lb. (12.3 kg.), has been walking for three months, and has no leg or hip deformity. Shoes with a medial wedge, worn for three months, have produced little change in the child's condition.*

Thomas C. Stevenson, M.D., Menlo Park, Calif.

Answer.—The prescribed treatment of a medial wedge on the medial border of the sole of the shoe should be continued until the child is 2 to 3 years of age; the wedge should be on the medial side of the heel as well as on the sole of the shoe. The mother should be instructed to manipulate the great toe and forefoot in the varus position daily, and the child should not go barefoot except in the evening when the mother can instruct him to walk on the outer side of each foot, with the feet turned inward. When the patient is 3 years old, some form of lift may be applied inside the shoe for support of the arch to prevent pronation.

IMMUNE MILK FOR ARTHRITIS

To the Editor:—*Please give me an appraisal of immune milk as a remedy for arthritis.*

J. H. Roberts, M.D., Cotati, Calif.

Answer.—Treatment with immune milk for patients with rheumatoid arthritis is based on several unproved hypotheses. It assumes that the disease is caused by deposition of an insoluble antigen in the tissues of the joints. The antigenic substance is assumed to come from streptococcic organisms. The streptococcic antibodies are produced in the cow by injection of a commercial polyvalent vaccine into the teat canal, prior to the cow's coming fresh with milk. When the patient ingests immune milk, it is also assumed that the antibodies are assimilated and when they reach the joints an antibody-antigen complex is formed.

In the instalment of "Primer on the Rheumatic Diseases" appearing in The Journal, Oct. 31, 1959, page 1210, the cause of rheumatoid arthritis is listed as unknown. That hypersensitivity may be a factor is mentioned, but this possibility remains in the realm of research. Treatment by means of streptococcic antibodies is not listed in the section on therapy.

Immune milk is not recommended as a therapeutic agent for the management of patients with rheumatoid arthritis.

FINGERNAIL GRAFTING

To the Editor:—The Journal *(92:1253 [April 13] 1929) contained an article by Sheehan about grafting a thumbnail. A patient has a similar problem that might be cured by this procedure. Could you supply additional information?*

M.D., Florida.

Answer.—I have studied this article several times and believe that the physiological principles it propounds and the treatment based thereon are sound and well carried out. A consultation with a plastic surgeon would be one source of information.

Answer.—I have never attempted to transplant a fingernail and do not know of anyone who has. If the procedure described in the above mentioned article were really successful, there would probably be other reports about it.

TREATMENT OF SPLIT FINGERNAILS

To the Editor:—The Journal, *April 18, 1959, page 1967, contained a question regarding a remedy for split fingernails. A successful method of treatment was published about 25 years ago in a yearbook of surgery. The two sides of the nail were sutured together at the distal end. I am not sure whether the surgeon drilled holes in the nail or simply used a needle to carry the thread through the nail. Additional sutures were placed in the nail as it grew out, and those put in previously remained in that portion of the nail which was subsequently trimmed. The article contained an illustration which showed the presence of at least two, and probably three, successive sutures present at the same time.*

Harry F. Becker, M.D., Los Angeles

Note:—Information on this question was identified in an article by Dr. Wilson A. Swanker entitled, "Reconstructive Surgery of the Injured Nail." The article was prepared by the *American Journal of Surgery* and published by the Yorke Publishing Company, Inc., New York.

PICA

To the Editor:—*A 2-year-old child eats paper—of any and all types. Please comment on the problem of children eating materials such as dirt, crayons, and paper.* *M.D., California.*

Answer.—The patient who eats paper has a disease that might be called papyrophagia; the nomenclature follows the established names, e. g., ingestion of dirt is chthonophagia and that of hair is trichophagy. The child should eliminate the paper with normal intestinal function since there is partial digestion of the cellulose constituents of paper. Depending on the amount of paper and the kind of ink consumed, the printer's ink may be a cause for concern. Ordinary paper without print can cause obstruction of the gastrointestinal tract by bolus formation, which would result in constipation and associated disorders. Eating of unusual materials frequently occurs in mentally retarded children. If the child is educable, all that needs to be done is to provide better supervision of his play and attention to his emotional needs. Since iron deficiency and infestation with intestinal worms can be organic causes for pica in children, a complete physical examination should be made.

BETA HEMOLYTIC STREPTOCOCCI AND PENICILLIN

To the Editor:—*Are there any authenticated instances of beta hemolytic streptococci which are resistant to penicillin?*

Arthur Koffler, M.D., Stamford, Conn.

Answer.—No authentic instances of beta hemolytic streptococci significantly resistant to penicillin appear to have been reported. Routine tests show some variation in the degree of sensitivity of different strains of hemolytic streptococci to penicillin, but this variation is not great enough to suggest significant degree of resistance. There is no reliable evidence of in vivo resistance to penicillin by hemolytic streptococcic infections that are not attributable to factors other than lack of sensitivity of the organism.

SPANKINGS

To the Editor:—*What is the current opinion about the disciplinary effect of spanking a disobedient child?* *M.D., New York.*

Answer.—Wholesome obedience from a child depends primarily on his love and respect for his parents, developed through the parent's devotion, reasonableness, firmness, and consistency. Punishment becomes necessary only when this system temporarily fails. Some parents rear well-behaved, well-adjusted children without administering any physical punishment; others (especially those who themselves were spanked occasionally in their childhood) naturally turn to this method. It is not harmful if the parents are generally fair and affectionate. A few parents use physical punishment excessively, because they are hostile or because they lack basic leadership and control, which is usually due to the fact that their own parents did not provide a good model of child-rearing. In the absence of mutual respect and other positive elements of good discipline, punishment is ineffective and often engenders further antagonism in the child-parent relationship. Spanking becomes clearly undignified and self-defeating when its use is extended to the adolescent.

The physician can be helpful not by arbitrarily approving or disapproving any one form of punishment used by his patients but by clarifying the problem of parent and child. When discipline fails completely, it is usually necessary to seek the aid of a family social agency or child guidance clinic.

INGESTION OF PLASTER OF PARIS

To the Editor:—*What symptoms will follow ingestion of powdered plaster of paris and what treatment can be recommended?*

M.D., New Jersey.

Answer.—The ingestion of plaster of paris (anhydrous calcium sulfate or dihydrate with about 5% of water [0.5 mol]) may result in obstruction of the patient's upper intestinal tract, particularly at the pylorus, because this compound hardens quickly after absorption of moisture. Treatment consists of giving glycerin or gelatin solutions or large volumes of water to delay the setting process; surgical removal of the material may be necessary.

CYANOSIS OF FINGERNAILS

To the Editor:—*What causes cyanosis of the nail beds in an otherwise healthy young woman? She has no cyanosis of lips, ears, or fingers or subjective complaints. There are no objective findings.*

C. J. Kilduff, M.D., Las Vegas, Nev.

Answer.—Cyanosis limited to the nail beds probably rules out systemic disease as a cause for the condition. Absorption of chemicals containing silver or aniline dyes may result in cyanosis of nail beds but will also cause extensive changes in skin color. Additional facts would be necessary for a specific answer to this question. Does cold bring on the cyanosis? Can it be relieved by placing the hands in warm water? Has it been present since birth or childhood? Is the cyanosis present constantly or is it relieved by certain factors? These facts would aid in determining whether localized vasospasm is a factor. Capillary microscopy might determine whether the patient has any congenital capillary or venule anomaly involving the vascular system of the nail beds. Cyanosis will disappear when pressure is applied to the nail with a glass slide; pigment in the nail will not. The patient's occupation may involve exposure to pigments or chemicals which can color the nail.

TREATMENT OF TYPHOID CARRIER

To the Editor:—*A 43-year-old man who had typhoid fever in 1938 moved to California in 1955, where he has had a variety of jobs, only the last of which involved the handling of food. What treatment, medical or other, is most effective in typhoid carriers?*

D. D. Carr, M.D., Las Vegas, Nev.

Answer.—Persons who have had typhoid fever may become temporary carriers up to six months after convalescence, when the condition may clear spontaneously. If the carrier status persists longer than one year, the patient is classified as a chronic carrier; two-thirds to three-fourths of these will continue indefinitely to shed bacilli from an infected focus, usually the gallbladder. They continue to do so, in spite of all other types of therapy, until the gallbladder is surgically removed.

When the nidus of infection is not the gallbladder, it is often in the solitary lymph follicles in the colon or in lesions in the small intestine. The bacillus sometimes persists in patients with nephrolithiasis, and as urinary carriers they are usually refractory to drug therapy.

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Typhus Bekämpfung in Südwesten Deutschlands, Arbeiten aus dem Kaiserlichen Gesundheitsampte, vol. 41, Berlin, Julius Springer Verlag, 1912.

SALIVA OF INCREASED VISCOSITY

To the Editor:—*A 48-year-old woman has complained for eight or nine months that her saliva is thicker and more sticky than usual and, at times, has a slightly whitish, discolored appearance. She is healthy and there is no evidence of swelling, infection, or neoplasm in the salivary glands. The results of a basal metabolism test were recorded at —12 to —15. Is this condition serious?*

Walter D. Hankins, M.D., Johnson City, Tenn.

Answer.—This woman has xerostomia, which is the absence or diminution in quantity of salivary secretions, causing a saliva of sticky consistency and difficulty in mastication and swallowing. On examination of the patient, the saliva usually "strings" when touched with a throat stick, and only a small amount of viscid saliva can be expressed from the principal salivary ducts.

Idiopathic xerostomia is a rare condition which is most commonly seen in elderly women. The onset is insidious, progressive, and, once established, permanent and irreversible. Treatment is limited to improvement in oral hygiene, the use of soothing mouthwashes, and improvement of nutritional status.

Acquired xerostomia is usually temporary, except when it occurs after radiation therapy. It may occur in patients improperly treated for dehydration, in patients with severe emotional disturbances, or in patients receiving drugs such as antispasmodics, antihistaminics, and opium derivatives. Treatment is directed primarily at the underlying disease or condition, with augmentation of the fluid intake induced by drinking unsweetened lemonade, chewing gum, or sucking juice from a lemon. Administration of nicotinic acid or pilocarpine hydrochloride may be of benefit.

A basal metabolism rate of —12 to —15 is probably not of any pathological significance in this woman, since she is completely symptomless with regard to her thyroid status.

POLYURETHANE PLASTIC FOAM FOR FRACTURES

To the Editor:—*Are there any drugs that can therapeutically stimulate formation of new bone? If not, is there some way to enhance formation of bone callus at the site of fracture, thus speeding the recovery of a patient?*

M.D., New Mexico.

Answer.—There appears to be no drug that has the specific pharmacological property of stimulating new bone formation.

There are many drugs that can be administered to correct specific causes of delayed healing, such as infection, abnormal calcium metabolism, and abnormal blood clotting mechanisms.

A substance that might be considered as decreasing the patient's period of immobility is polyurethane plastic foam (Ostamer), which is a strong plastic used to bind and stabilize fractures of the long bones of the upper or lower limb. It is used in fractures requiring open reduction and must be forced into the medullary canal in both directions from the site of the fracture to produce and maintain good fixation. The plastic foam supposedly acts as a framework for growth and repair of new bone by which it is replaced.

However, use of this substance seems to offer little in the routine management of fractures and other orthopedic problems that cannot be accomplished equally well by standard methods. Considerable technical problems attend its use; some physicians have reported a high incidence of complications. Consequently, it has been suggested that, until further experience is acquired, it be reserved for trial in carefully selected cases, such as of nonunions that have not healed despite several competent bone grafts, or of pathological fractures caused by metastatic malignant tumors.

WASHINGTON NEWS

Drug Industry Hearings . .
Administration Weighs Medical Plans . .
Keogh Bill Prospects . .

DRUG INDUSTRY SPOKESMAN CITES PROGRESS; SCORES CRITICISM

The president of the Pharmaceutical Manufacturers Association told Congress that the drug industry has served the public interest by driving prices down to the lowest possible level. "Americans would be paying a billion dollars a year more for drugs if the price of medicine in the past few years had gone up only as much as the total cost of living," said PMA President Dr. Austin Smith.

Testifying before the Senate antimonopoly subcommittee headed by Sen. Estes Kefauver (D., Tenn.) as it resumed its hearings on drug prices, Dr. Smith criticized charges leveled against drug companies at subcommittee hearings earlier this year. "There is grave danger," he said, "of misinforming the public when attention is directed toward the single product of a single company . . . without relating these to the many thousands of products produced by the entire industry."

Since 1947, the industry has spent about 1 billion dollars in research alone, Dr. Smith pointed out, adding that the major risks in the field must be met out of profits. In 1958, out of 114,600 substances tested, about 40 became marketable drugs—a failure ratio of 2,865 to one. Also, competition rapidly obsoletes a marketable drug, the witness noted.

Replying to accusations of huge profits, Dr. Smith said that between 1948 and 1958, for example, wages rose 70% and construction costs 64%, while wholesale drug prices went up only 3%.

As for advertising, "Ours are about the only ads in America that tell not merely the good things about our product, but deal exhaustively with the bad ones as well. Toxicity, side-effects—all must be exposed in full detail. Some, of course, are 'reminder ads,' intended to recall to the reader's memory the more extensive clinical findings he has seen earlier.

"But the most important advantage of medical advertising is that it brings new product information to the doctor's attention almost as soon as the new drug has received approval by the Food and Drug Administration. This is not true of scholarly articles which appear in the editorial content of medical journals. The time lag here ranges between six months and a year."

Here are some of Dr. Smith's statements on other important aspects of medical practice and drugs:

Detail Men: Surveys have shown that the detail man is the physician's first and most important source of new product data. The benefits of detailing are not matched by any other medium. In a few minutes the detail man can acquaint the doctor with the capacities and the limitations of a new drug.

Aids to Medical Practice: Educational funds support a large part of most medical society programs through journal advertising and exhibit space. They contribute substantially to the economic existence of most medical journals . . . provide almost all available closed-circuit educational TV for physicians . . . provide medical teaching films, circulation of reprints of medical reports, medical seminars, and finance millions of samples used by doctors to determine their patient's response to a drug before the patient spends money to fill a prescription.

Generic Terms: Under the American system of medical care, the physician alone arrives at the diagnosis and he alone decides precisely what drug is to be prescribed for his patient . . . From the standpoint of the physician and pharmacist, the use of generic equivalents would in no way lessen but might well increase their liability, because it could increase the chances for unfavorable reactions, to the detriment of the patient. . . .

Competition: . . . . I find it paradoxical that on the one hand our industry is charged with being noncompetitive, while at the same time our advertising and promotion—use of time-tested American instruments of competition—are singled out for special criticism.

HIGH-LEVEL STUDY ON FORAND BILL ALTERNATE

There were increasing signs that the administration has decided to push for some type of program in the field of health care for the aged this year.

Of five plans reported to be before the budget bureau and White House for consideration, four involved hiking social security taxes to finance partial medical and hospital care for aged social security beneficiaries. Although this also would be done under the disputed Forand Bill calling for government medicine, the administration plans allegedly would allow the states to administer actual operation of the aged aid programs. Under the Forand measure, of course, the federal government would operate as well as finance the scheme. It is opposed, by the American Medical Association and many other groups, as a first step toward a complete federal medical setup in this country, among other objections.

Another plan receiving top-level administration study, according to reports, would provide a 90-million-dollar program of federal grants to help the states to expand their present public assistance programs for indigent older persons.

(Continued on next page)

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Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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Arthur S. Flemming, Secretary of Health, Education, and Welfare, has asserted frequently that he planned to send Congress an aged health bill this session, but at the same time he has reiterated the administration's opposition to the Forand-type approach. Generally speaking, any plan that would use the federal social security mechanism for financing has been regarded as a Forand-type bill, since it involves compulsory social security contributions.

The reports of administration consideration of these plans were neither officially confirmed nor denied by the administration as of this writing, but high sources confirmed them informally.

The alternatives involving the social security program would cost an estimated 400 million to 1 billion dollars a year derived from higher Social Security taxes. The Forand bill to expand the social security program to include partial financing of some health care for aged beneficiaries would cost about 2 billion dollars annually.

What effects submission of any administration program would have on Congress was a matter of conjecture, but some observers said it would probably touch off a full-scale debate on the entire matter of federal intervention in the private practice of medicine. The House Ways and Means Committee was scheduled to consider changes in the social security program at closed-door meetings in late March.

PROSPECTS BRIGHT FOR SELF-EMPLOYED RETIREMENT BILL

The Senate Finance Committee charted a March session on legislation to encourage the self-employed to set aside money for retirement. Lawmakers predicted that a majority of the Senate favors the measure.

There were indications that the bill might be brought up for action in the near future, although exactly what form it would take was uncertain. The House last year overwhelmingly approved the bill sponsored by Rep. Eugene J. Keogh (D., N. Y.) and the late Rep. Richard M. Simpson (R., Pa.). The Senate Finance Committee, led by Sen. Harry F. Byrd (D., Va.), held hearings on it last year but took no action, in part because of administration opposition.

The bill is designed to give self-employed persons like physicians, dentists, lawyers, and farmers tax treatment similar to that now provided salaried persons. Corporation contributions, often 100%, are tax deductible, but there is no tax deduction or deferral for persons who are in business for themselves.

Under the House-passed bill, self-employed persons would be entitled to tax deferrals on up to $2,500 a year or 10% of net income. A maximum of $50,000 could be set aside over a lifetime, provided the money was invested in qualified retirement plans. The tax would come into effect when the person started drawing his retirement money.

There were some signs that the administration might be softening its opposition to the bill, based primarily on the immediate loss of tax revenue to the government. Administration officials have backed the principle of the measure.

A new proposal was being considered in high quarters that would eliminate one of the arguments raised against the bill—that it did not cover employees of self-employed persons. The proposal would require establishment of retirement plans for such employees if the employer wished to come under the bill's tax deferral program.

The American Medical Association and hundreds of organizations representing small businessmen and other self-employed persons have urged approval of the tax deferral plan. They said it would encourage individual initiative and free enterprise by spurring retirement security similar to that offered in large industries.

MISCELLANY

President Eisenhower vetoed the first major bill of the session—a measure to raise to 900 million dollars the present 10-year ceiling of 500 million dollars on federal spending to curb water pollution. "Because water pollution is a uniquely local blight, primary responsibility for solving the problem rests not with the Federal government but rather . . . state and local governments," said President Eisenhower.

Arthur S. Flemming, Secretary of Health, Education, and Welfare, urged the automobile industry to equip all new cars with a device to reduce fumes but opposed a measure that would make such installation mandatory. "If it has been established that an action can be taken to reduce the menace of air pollution, I think that action should be taken," Flemming told a House commerce subcommittee. Automobile company officials told the subcommittee that the device, which eliminates crankcase gases but not exhaust, could be installed for as little as $10 on new cars.

The U. S. Public Health Service and the American Hospital Association announced formation of a 15-member special committee to develop principles for community-wide health facility planning. The committee, composed of authorities in the hospital and health facility field, will be headed by George Bugbee, President of the Health Information Foundation.

Dr. Arnold B. Kurlander was promoted to the post of assistant surgeon general of the U. S. Public Health Service, a newly established office. Dr. Kurlander will be responsible for providing immediate assistance to the surgeon general on current programs and will also help handle communications between the service's four bureaus and the surgeon general's office. Dr. Kurlander is a native of Cleveland.

Byron E. Harter, administrative assistant since 1950 to Rep. William M. McCullough (R., Ohio), was appointed congressional liaison officer for the Department of Health, Education, and Welfare. He succeeded Robert A. Forsythe, who was named HEW assistant secretary for legislation.

A conference of seven western state officials and officers of the Public Health Service was held in Phoenix, Ariz., to discuss federal enforcement procedures in controlling pollution of interstate waterways. The objective was a thorough study and clean-up of the Colorado River system, which drains about one-twelfth of the land area of the U. S. One of the subjects dealt with was radioactive contamination from uranium milling operations.

A new crackdown on abuse of amphetamines, or "pep pills," is being prepared by HEW. HEW Secretary Flemming said the agency is seeking to have amphetamines placed in the same category as narcotics, which would necessitate the registration of all sales.

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SOCIETY	PRESIDENT	SECRETARY	MEETING
American			
Public Health Association	Malcolm H. Merrill, Berkeley, Calif.	Berwyn F. Mattison, 1790 Broadway, New York 19	San Francisco, Oct. 31-N
Radium Society	Theodore R. Miller, New York 16	R. L. Brown, Robt. Winst	Juan, P. R., Mar.
Rheumatism Assn.	Charles J. Smith, Denver	Mr. G. W. Speyer, 580	mi Beach, Fla., Jun
Roentgen Ray Society	Barton R. Young, Philadelphia.	C. Allen Good, 200 1st	ntic City, Sept.
School Health Assn.	Lyda Smiley, M.A., La Mesa, Calif.	A. O. DeWeese, 515 E.	Francisco, Oct.
Society for Clinical Investigation	Robert W. Berliner, Bethesda, Md.	S. J. Farber, 550 1st Ave., New York 16	Atlantic City, N. J., May
Society for Experimental Pathology	Cyrus C. Erickson, Memphis, Tenn.	J.F.A.McManus, Univ. of Ala. Med. Center, Birmingham, Ala.	Chicago, Apr. 11-15
Society for Pharm. & Ex. Ther.	Louis S. Goodman, Salt Lake City.	K. H. Beyer Jr., Merck Sharp & Dohme, West Point, Pa.	Chicago, April
Society for the Study of Sterility	Charles Lee Buxton, New Haven, Conn.	H. H. Thomas, 920 S. 19t	
Society of	Hand, Newton Highlands, Mass.	Mr. J. W. Andes, 188 W.	
Society of	d G. Wood, Cleveland.	Frank W. Putnam, U. of	
Society of	Clemmer, Albany, N. Y.	Mr. Claude E. Wells, 445	
Society of	Goss, Seattle	Mr. Robt. L. Richards, 3	
Society of	M. Epsteen, Chicago.	E. C. Hinds, 1508 Medica	
Society of	h L Pickrell, Durham, N. C.	Thomas R. Broadbent, 50	
Society of	Wright, Sc.D., Washington, D. C.	R. B. Hill, 3575 St. Gau	
Surgical Assn.	H. Cole, Chicago.	W. A. Altemeier, Cincinn.	Apr. 3-6
Therapeutic Society	Charles L. Leedham, Cleveland.	Oscar B. Hunter Jr., 915-19th St., N.W., Washington 6, D.C.	Miami Beach, Fla., June
Trudeau Society	Roger S. Mitchell, Denver.	Mr. F. W. Webster, 1790 Broadway, New York 19	Los Angeles, May 16-19
Urological Assn	William M. Coppridge, Durham, N. C.	Samuel L. Raines, 188 S. Bellevue Blvd., Memphis, Tenn.	Chicago, May 16-19
Veterinary Medical Assn.	S. F. Scheidy, V.M.D., Bryn Mawr, Pa.	H. E. Kingman Jr., 600 S. Michigan Ave., Chicago 5	Denver, Aug. 15-18
Assn. for Research in Nervous & Ment. Dis.	Lee Eaton, Rochester, Minn.	Rollo J. Masselink, 700 W. 168th St., New York 32	
Assn. for Research in Ophthalmology	James H. Allen, New Orleans	Lorand V. Johnson, 10515 Carnegie Ave., Cleveland 6	Miami, June 12-17
Assn. of American Medical Colleges	Thomas H. Hunter, Charlottesville, Va.	Richard H. Young, 303 E. Chicago, Chicago 11.	Hollywood Beach, Fla., O Nov. 2
Assn. of American Physicians	William B. Castle, Boston.	P. B. Beeson, Yale U. Sch. of Med., New Haven 11, Conn.	Atlantic City, N. J., May
Assn. of Life Ins. Med. Dir. of America	Ennion S. Williams, Richmond, Va	Royal S. Schaaf, P. O. Box 594, Newark 1, N. J.	New York City, Oct. 19-21
Assn. of Medical Illustrators.	Mrs. A. B. Maller, Chicago.	Miss Rose M. Reynolds, 42nd and Dewey Ave., Omaha 5.	Chicago, Oct. 3-5
Assn. of Military Surgeons of U. S.	R/A Richard A. Kern, Philadelphia.	R. E. Bitner, 1726 I St., N	Oct. 31-
Assn. of Public Health Phys.	Sanford P. Lehman, Seattle	Joseph M. Bistowish, P. O.	
Assn. of State & Territorial Health Officers	Wilson T. Sowder, Jacksonville, Fla.	Andrew C. Offutt, 1330 W.	
Biological Photographic Assn	Mr. Y. Y. Yamamoto, Des Moines	Miss J. Waters, Box 1668,	22-25
Central Assn. of Ob. & Gyn.	Isadore Dyer, New Orleans	H. L. Gardner, 633 Herman	
Central Neuropsychiatric Assn.	Martin H. Hoffmann, Detroit.	R. M. Patterson, Ohio S. Uni	Oct. 1
Central Society for Clinical Research	John H. Dingle, Cleveland	Austin S. Weisburger, 2065	
Central Surgical Assn	Charles D. Branch, Peoria, Ill.		
Clinical Orthopaedic Society	Fred C. Reynolds, St. Louis		
College of American Pathologists	Frank C. Coleman, Des Moines, Iowa		
Gerontological Society	Nathan W. Shock, Ph.D., Baltimore.		7-12
Industrial Medical Association	D John Lauer, Pittsburgh		pr. 25-
Internat'l Coll of Surgeons, U S. Section	Edward L. Compere, Chicago.		
Interstate Postgrad Med. Assn. of N. A.	Robert M. Zollinger, Columbus, Ohio.		ct. 31-Nov. 3
Medical Library Assn.	Miss Mildred Jordan, Atlanta, Ga		Mo., May 1
National Medical Assn.	E. C. Mazique, Washington, D. C.		ug. 8-11
National Med Found for Eye Care	Ralph O Rychener, Memphis		9
National Multiple Sclerosis Society	Mr. Ralph C. Glock, New York		r. 8
National Proctologic Assn.	Peggy Cornet, Chicago Heights, Ill.		
National Tuberculosis Assn.	H McLeod Riggins, New York 19.		5-20
Neurosurgical Society of America	Collin S MacCarty, Rochester, Minn.		Calif., N
Radiological Society of North America	T. J. Wachowski, Aurora, Ill.		9
Society for Investigative Dermatology	Thomas B. Fitzpatrick, Boston.		June
Society for Pediatric Research	Henry L. Barnett, New York 61		May 3-
Society for Vascular Surgery	Richard Warren, Boston.		12
Society of American Bacteriologists	Charles A. Evans, Seattle		May 1-5
Society of Biological Psychiatry	Paul Hoch, New York City		Fla., June
Society of Clinical Surgery	James Priestly, Rochester, Minn.		
Society of Neurological Surgeons	Paul C. Bucy, Chicago.		le, Apr. 18-19
Society of University Surgeons	Henry T Randall, New York 21		
Southeastern Surgical Congress	B. T. Beasley, Atlanta, Ga.		Orleans, Mar. 21-24
Southern Medical Assn.	Edwin H. Lawson, New Orleans.		ouis, Oct. 31-Nov. 3
Southern Surgical Assn	Francis M. Massie, Lexington, Ky.		Raton, Fla., Dec.
Southwestern Medical Assn.	Russell L. Deter, El Paso, Texas	izona St., El Paso,	Paso, Oct. 20-22
Southwestern Surgical Congress	Fred H. Krock, Fort Smith, Ark.	Arts Bldg., Oklahom	r., Mar. 2
Student American Medical Assn	Mr. W. R. Kirkham, Oklahoma City	Mr. Russell F. Staudacher, 430 N. Michigan,	May 5-8
The Endocrine Society	Dwight Ingle, Chicago.	H. H. Turner, 1200 N. Walker St.	Fla., June
	Thormley, Fresno, Calif.	R. M. Brundage, Atomics Internat	Oct. 7-9
		Miss Vi Mathiesen, 354-21st St.,	
		Kenneth A. Blinn, 4120 Atlantic A	Diego, Oct. 23-27
	Priestley, Rochester, Minn.	John T. Reynolds, 612 N. Michigan	
	ank Gastineau, Indianapolis.	Miss Margaret Wolfe, 535 N. Dearborn St., Chicago 10.	Miami Beach, June 13-17
	Lemieux, Quebec.	Louis H. Bauer, 10 Columbus Circle, New York 19.	West Berlin, Sept. 15-22

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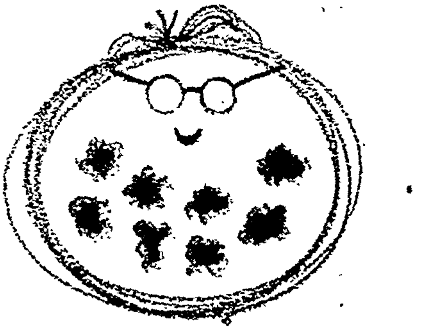

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RESEARCH IN PREVENTIVE MEDICINE

Thomas Francis Jr., Ann Arbor, Mich.

The aim of preventive medicine is the prevention of disease, and the issue is beclouded when the importance of a disease is measured in terms of the resultant deaths. True prevention includes protection from chemical and physical exposure, correction of dietary deficiencies and excesses, and prevention of infectious diseases. The common assumption that infectious disease has been conquered is false. The Armed Forces Epidemiological Board, established in 1941, with 12 commissions and 180 senior investigators, has been able to make many major contributions. These would scarcely have been possible in other than military populations, but the results have been valuable to the civilian population as well. Research in medicine for the future must be directed toward the prevention of the common annoying chronic diseases.

PREVENTIVE medicine is at present a diffuse term meaning different things to different persons. At times it appears no longer to possess a central theme or phiosophy. A change in name, as some have sugested, would bring little benefit since it might urther obscure the intent. At times the field apears to be interpreted so broadly that care of the ck and disabled—that is, supportive and recontructive medicine—occupies more attention than he primary objective. Of course, all of medicine, nd I mean all sciences contributing to medicine, as a preventive aspect. But the virtue of preventive medicine lies in the concentration of attention n the maintenance of health and the prevention of isease. As Alan Gregg expressed it, "Preventive edicine has the charm and bewilderment and the pportunity of being virtuous, because applying reventive medicine is behaving as we should beave in the light of what we know of the vast apacities of medical science." Perhaps our comlaints that preventive medicine is not fully appreiated tie in with the realization that virtue is not asily maintained and that we think as we live. Our roblems of recruitment may relate to the fact that e spend more time in expounding virtue than in eveloping it.

Concept of Health

Man's progress toward civilization has been losely intertwined with his development of measres to protect life. Some of the adversaries could be recognized even by primitive man, since they related to human behavior and aggression, but disease was understood only as a harmful effect of certain associations revealed by experience. The level of our current knowledge is not much more advanced. Descriptive information has increased

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Read at the meeting of the American College of Preventive Medicine, Atlantic City, N. J., Oct. 21, 1959, during the tenure of the Third Annual ectureship in Preventive Medicine.

From the Department of Epidemiology and Virus Laboratory, School of Public Health, University of Michigan.

tremendously, but we have gained only a slight foothold in understanding the mechanisms involved in disease processes. The concept of a specific causative factor has been amply demonstrated but constantly challenged in cases in which the etiology of a disorder is yet unproved. We have derived empirical knowledge and procedures with which to limit the incidence or reduce the severity of some disorders, while others increasingly mount the walls of our ignorance. It is obvious that we have more effectively eliminated the buffalo, the whooping crane, and the trailing arbutus than we have obliterated the causes of disease. It is true that some regions of the world are gaining in this struggle; but in other areas unrelieved burdens still exist that constitute continued risks to health and peace in this mobile, shrinking world. Conversely, certain disorders of increasing damage to the longer-lived, more favored populations appear to be diminished by the conditions of life in crowded areas of economic want; this emphasizes the relativity of health, global or individual, and points out that we are scarcely on the threshold of understanding the problems of either health or disease.

Man is, above all, a biological creature living in environments which expose him to an endless array of potentially pathogenic agencies. The effects of some of these are known, but new ones arise as our explorations of the universe enlarge, as we disturb natural adjustments, as we synthesize new products and new conditions of existence, and as we change our way of life. It cannot be expected now or later that a functioning community can be devised which is spared from all harmful exposures—like germ-free animals maintained in stress-proof isolation.

Health, then, may be considered a state of adequate structure and function, with adequate reserves. This state is being constantly bombarded by innumerable potentially pathogenic stresses, so that each person is in a state of potential disorder. The outcome depends on the ability of the person's reserve to absorb the stress without depleting his range of tolerance, or to respond with additions to his reserve to enhance health and resistance to the harmful influence. It is readily apparent that small shocks might be effectively buffered, while excessive insult or continued exposure might well break through. Variation in the threshold of tolerance among individual persons and at different ages is also easily pictured. Conversely, disease is a reaction to a stress which extends beyond the bounds of individual reserve and adaptability. (This can also be applied to a community.) In this sense, we would measure disease or disease potential in terms of health rather than defining health in terms of disease, and our efforts would be directed toward preservation of the norm.

Unfortunately, the available measurements of health are few. Despite bold efforts to proclaim a theme of "positive health," little information regarding the maintenance of health which has not derived from recognition that a certain procedure prevented disease exists today. Consequently, we have no adequate body of measurements of health that are not based on the absence of a disorder. In fact, we describe our present health activities as vaccination against smallpox, use of fluorides against dental caries, or something that is "good" for heart disease. Our current ability to detect and identify disorders depends largely on their severity; what we consider incipient is an already far-advanced biological imbalance. Our so-called health statistics are commonly disease or death statistics. In fact, one of our most disturbing practices is to consider the importance of a disease in terms of resultant deaths as if we were somehow to evite the inevitable. We split life and the family into convenient specialist categories to make the recording of a sequential comprehensive view of the individual person's or group's experience difficult. We witness the tendency to move bithely under the cover of a slogan or in response to the call of the huckster to realms of custodial care or administrative busyness with the end-stages of disorder, while we withdraw from profitable investigation and exploitation in the areas of their causation and prevention. It must be constantly repeated that research is the only hope for the development of preventive medicine—and now I am speaking of preventive medicine literally—namely, prevention of disease. Research offers a new face to the field of practice.

Areas of Preventive Medicine

The areas of true prevention now available may be summarized under three headings.

First, protection from chemical and physical exposure. This applies particularly to occupational health—one of the oldest and a continued area of interest.

Second, prevention by correction of dietary deficiency or excess. This area has a steady range of development as knowledge of the specific significance of various components becomes known and processing changes the character of natural foods.

Third, prevention of infectious disease by specific measures and sanitary social procedures. A limited number of severe, epidemic communicable diseases are effectively prevented by specific vaccination. A few bacterial infections can be prevented by drug or antibiotic therapy, if properly used. Some are limited by sanitary barriers under stable peacetime conditions or by environmental control. Entirely new agents of large epidemic potential are being recognized, and still others can be expected, but none has been eradicated.

Genetics is a field in which knowledge is increasing but which, as yet, is put to limited use in preventive procedures.

The tendency of preventive medicine to move away from unfinished business is nowhere more clearly emphasized than in the field of infectious disease. And nowhere is there a more precarious balance with respect to present preventive procedures. The return of the staphylococcus and other resistant organisms, the development of new antigenic strains, the reliance on sanitary facilities which can be easily disrupted, the ready possibility of importation of infections, the recurrence of epidemics when vaccinations are not thoroughly applied—all emphasize the narrow margin of safety in our safeguards.

The commonly repeated assurance that infectious disease is conquered is simply not in keeping with the evidence. This is emphasized in the compilations of incidence and death presented by Halbert Dunn in "Health and Demography" (1956). Up to 45 years of age, the 12 leading causes of illness are infections, with the exception of accidents, some "functional" digestive disturbances, and some of the disorders of the genital tract and breast in women aged 15-45 years. Beyond the age of 45 years, infection still constitutes a major factor as the immediate cause of illness, although an increasing amount of illness relates to disorders which are referred to as noninfectious.

The United States National Health Survey reports that in the year July 1957-June 1958 45% of all bed-disability days, 36.5% of work-loss days (for persons 17 years and older), and 67% of school-loss days (for persons aged 6 to 16 years) were caused by acute respiratory illness alone. Respiratory disease was responsible for 60 to 66% of the incidence of acute conditions recorded in every age group. In comparison with a total of 764 million days of bed disability caused by all chronic conditions in the United States in one year, there were 593 million from acute respiratory disease alone (see table). The work-loss figures in days for the year were 219 million from respiratory disease and 226 million from circulatory, digestive, and arthritic disease and impairments from injury or other origin combined. The average number of days lost by the usual working population from acute conditions was 5.98 and from all chronic conditions 6.52. These data represent the noninstitutionalized population of the country.

Areas of Research

The examples given clearly present to preventive medicine its continued responsibility in those areas of research dealing with the great body of day-by-day infections which repeatedly interrupt healthy, effective life. They probably are also significant factors in the etiology of other disorders whose origins and causes are as yet poorly defined. In addition, they are leading causes of death during the most vigorous periods of life, from the school years through 44 years of age. The point to emphasize, however, is that research must be increased and maintained in the area of the common, annoying disorders of health, in which the preventive promise is high. Human mortality is still 100%; thus, while death is inescapable, these disturbances can be prevented.

The maintenance of effective health is nowhere in our scheme of life more actively required than in the military services. In the first place, the population involved is selected with care for its healthy status, and if it is to fulfill its functions in training or in operation, those disturbances most commonly disruptive of daily health must be controlled. As would be expected, they comprise primarily the acute diseases of young adult life and accidents. During 1958, the rate of total "excluded-from-duty" admissions to hospitals and quarters in the United States Army was 397 per 1,000 per year. The incidence of acute respiratory infections was 160, representing 46% of all admissions for disease and 40% of all nonbattle causes. Accidents were the next, with a rate of about 53 per 1,000 per year. But, in addition, the recorded incidences of 24 for the class of infective and parasitic diseases, 16 for gastroenteritis, and 15 for urinary and male genital disturbance, rheumatic fever, and others indicate another large group of infectious diseases. With its far-flung geographic dispersions and the increased risks attendant on wartime activities, the military services must also be constantly alert to other common disease problems that are largely avoided at home under conditions of peace and stability. Continued research into etiology, pathogenesis, and prevention of these ordinary diseases is essential, if effective manpower is to be sustained for military operations. It is an old saying that the medical lessons learned in one war are forgotten in the intervals of peace. There has always been a small body of devoted men who have sought to prevent this gap almost by individual effort, just as individual persons or small groups of investigators in civilian agencies have maintained progressive inquiry into specific infectious diseases. But the necessity for coordinated, continuing research which is directed toward prevention of these repetitive and persistent infective urchins has been realistically supported in few quarters.

*Number of Days of Disability per Year per Group of Conditions**

	No. of Days of Disability per 100 Persons			
Conditions	Restricted	Bed Disability	Work Loss†	School Loss‡
Acute respiratory	696	352	367	565
Chronic				
Circulatory	288	99	116	6
Arthritis and rheumatism	152	40	52	...
	No. of Days of Disability per Million Persons			
Acute respiratory	1,172	593	219	196
Chronic				
Circulatory	484	167	69	2
Arthritis and rheumatism	255	67	31	...

* Data taken from Reports of National Health Survey.
† Age 17 yr.—"usually working" persons.
‡ Age 6-16 yr.

U. S. Armed Forces Research Commissions

An outstanding example of sustained effort toward understanding and preventing common disorders is the Armed Forces Epidemiological Board. It was established in January, 1941, through the energetic foresight of the late Steve Simmons, chief of preventive medicine, with the aid of the surgeon general of the Army, Magee, and the guidance of the president of the board, Francis Blake, and the administrator, General Bayne Jones. Expansion of the Army had been accompanied, as always, by an increase in the incidence of respiratory disease. The objective, as stated, was "to appoint and maintain a board for the investigation of the etiology, epidemiology, prevention, and treatment of influenza and other acute epidemic diseases in the Army" and to prepare in time of peace for exaggerated risks of wartime mobilization and operation. The organization was to consist of a central board, an additional group of expert scientists who could meet with the board, and investigative teams who could go to military stations for study and control of epidemics. It was emphasized that the organization should be flexible and not hampered by unnecessary administrative delays. The investigative units were termed commissions, and their major focus of concentration was respiratory disease, as evidenced by their names: the commissions on acute respiratory disease, on hemolytic streptococcic infections, on influenza, on mumps and measles, on meningococcic infection, on pneumonia, on cross infections in hospitals, and on epidemiologic survey. In addition, there were commissions on neurotropic virus diseases and on tropical diseases. Their personnel comprised 111 civilian medical scientists who were already engaged in research on these problems.

I recall the extended discussions at the early meetings about whether or not the commissions should serve only as fire-fighting units on call for emergencies in military situations. Although these sporadic excursions could be of aid, the need for continuity in the study of disease problems for fundamental research in microbiology and immunology and for supplementation of military facilities by university and other laboratories was clearly recognized. It was concluded that programs of intensive study must be sustained if the potentialities and the functions of the board were to be effectively met.

The contributions of the board and its commissions during World War II were such as to elicit the signal statement of one judge, that "No one ever got so much, buck for buck, in returns." By attracting and supporting the activities of groups of collaborating specialists, the commissions of the board became focal concentrations of expert knowledge and effective investigation of various diseases on a world-wide scale. It is a pertinent point, however, that it was the common infectious diseases of the area which required the concentrated attention of investigators—whether in the continental United States or in overseas locations.

The normal expectation was that the organization would be disbanded at the end of the war, but the demonstrated value of the commission's approach and the assistance thus available to the U. S. Armed Services was appreciated. It was redesignated the Armed Forces Epidemiological Board, as a Department of Defense agency, to serve the surgeons general of the Army, Navy, and Air Force for consultation on field problems, for field investigations, and for research in preventive medicine. While certain commissions have been discontinued or combined with others, new commissions have been formed, with an epidemiologic orientation toward special and persistent problems of preventive medicine.

At present there are 180 senior investigators officially attached to the board and its 12 commissions. In association with each responsible investigator, several more members of his staff usually participate in the research which the laboratory is pursuing.

Accomplishments of Commissions

I shall not attempt to recount all the accomplishments of the board nor to make expansive claims they are not necessary. What is to be emphasized is that many of these accomplishments would scarcely have been possible had the studies not been made in military populations, with the aid of military scientists and physicians.

In the field of respiratory disease, major contributions in which the commissions have participated include the dynamics of meningococcic herd infections and their chemoprophylaxis; the spread and control of streptococcic infections and their sequelae; the development and application of an effective influenza vaccine, and the establishment of extended listening posts for detection and study of influenza viruses; the epidemiology of atypical pneumonia as a disease of recruits, basic demonstrations of its viral etiology, and later studies of adeno vaccine effectiveness; further field demonstrations of immunization against pneumococcic pneumonia with polysaccharides; the demonstration of new respiratory viruses and their associated clinical reactions; studies toward development of vaccines against measles and mumps; the development of an effective vaccine against Q fever; intensive studies of the ecology and control of infection by Coccidioides immitis; and improvement in smallpox vaccine.

Major contributions have been made to the knowledge of and efforts to control infectious and serum hepatitis; to the identification of dengue and Phlebotomus-transmitted viruses and possible vaccines; and to identification of various encephalitic viruses, their serologic relationships, and vaccine development. Investigations into the principles of natural resistance; into the development, evaluation, and improvement of immunizing procedures; into mechanisms of infection; and into the disease process of such time-honored "old soldiers" as dysentery, typhoid, and cholera, which have not yet faded away, continue. In fact, the entire field of diarrheal diseases is under study, with attention to procurement of better information about the physiological basis of susceptibility and the pathogenic capacity of the agent. Studies of cutaneous disorders—sensitizations, acne, itching, poison ivy, fungal infections, i. e., the ordinary ones—are yielding basic etiological and prophylactic information.

Those studying rickettsial disease represent almost the only remaining nucleus of investigators in the United States, their activities continuing in fundamental research as well as in discovery of improved preventive measures or treatment. Their contributions to the knowledge of the milder form of epidemic typhus or Brill's disease, Tsutsugamushi fever (scrub typhus), and Q fever and to corresponding control measures have been outstanding. Much the same is true of the Commission on Parasitic Diseases with respect to malaria and schistosomiasis; they seek to maintain a corps of competent diagnosticians and scientific experts in the military services especially, but their work turns again to basic research for greater biological information. Studies in environmental hygiene have provided data regarding pollution and the disposal of waste in Arctic areas, adaptation to warm climates, food control, and occupational protection. The influence of low-grade radiation on infection and resistance is being investigated.

The Commission on Accidental Trauma, adapting the epidemiologic approach to an important study of the role of the driver, the machine, and the environmental state has served as a focal point for interested groups who were otherwise isolated. They have had a definite influence on the consideration of safety features and on the search for measures to eliminate the hazardous driver. Although the military importance of accidents, both civilian and military, in motor vehicles is fully demonstrated, there are strong currents of resistance to the serious study of the institution of preventive measures. Nevertheless, the board has taken an important national leadership in creating an effective front of research into the problem of vehicular accidents especially.

One other area of known importance that has been sporadically studied is that of the relation of military housing to infectious and mental disturbances. With every increase in strength of military personnel, platitudinous surveys of the housing problem are made. Each change in barracks is made with little or no advice on the aspects of medical or health engineering. It is obviously a zone for extended study, but fatalism and jurisdictional authority interfere.

The research activities have been financed primarily through U. S. Army medical funds, although the other services have contributed to the support of certain specific investigations. Moreover, extended field studies have been conducted in U. S. Air Force and Navy installations. The individual investigators receive their funds on a contract basis after consideration and recommendation by one of the commissions, approval by the central board, and administrative concurrence by the service. At times, if funds are scarce, additional money may be sought from other agencies for a recommended activity, while affiliations and sponsorship by the commission are retained. The commissions do not propose to act as study sections or as granting agencies or to preempt control of an area of research. Their purpose is to gather into a mutual working relation military and civilian scientists with common interests and the dedication to work toward the solution of a given problem. By close adherence to the preventive medicine divisions of the three services, attention to the military needs can be steadily maintained. Disease situations which require investigation, difficulties in application of recommended measures, and future projections of the work accomplished can be brought forward for consideration by the appropriate commissions. But the areas of study are not laid down purely as military edicts; the scientific approach is largely devised by the scientific judgment of the experts in that field. In effect, each commission constitutes a research institute with a director, even though housed in laboratories of the affiliated investigators, in military installations, or in other institutions which may be sites of study.

Although the orientation is toward military preventive medicine, the entities under study are also the common causes of disability in the civilian population. Consequently, benefits are mutual and those who are benefited are our sons and daughters. Moreover, there is a great conviction among the participants in this work, as scientists and citizens, that the sustained studies are necessary if these problems of preventive medicine in the U. S. Armed Forces are to be met rather than ignored.

Need for Research Commissions in Preventive Medicine

The reason for this expanded discussion of the Armed Forces Epidemiological Board is (1) to emphasize the limited attention now given to coherent study of certain ordinary disorders and (2) simultaneously to point out how an amount of money, small in current terms, but invested in sympathetic support of a sustained united effort, can earn rich dividends. The "commission" plan of investigation recommends itself not merely as a source of expert opinion but as a unit of action research. It should not be an intellectually closed corporation but a collection of balanced judgment and study. It provides the means of encompassing, in a coherent fashion, research on numerous facets of a problem on which information is needed. This information can then be collated, critically evaluated, and projected in an environment of collaborating experts. Dictatorial or financial control of research is avoided by giving the direction of research to the researchers. It retains freedom for individual initiative within a framework of common purpose and objective. In fact, it can often provide support for new adventures which by themselves might wither. Flexibility and versatility permit a change in direction from the concentration on epidemiologic observation to fundamental study of reactions of the host or of the pathogenic agency, as indicated. The commission can provide continuity to research while deriving benefit from new or brief excursions into other areas and can buffer the disturbances of progress occasioned by hucksters and the promoters of expediency. An agency like the Armed Forces Epidemiological Board could well be expanded to deal with other problems and to serve more widely in the national need for research in preventive medicine. It can be a model for advance in difficult and little-understood problems of many kinds. It is my recommendation that, in the planning for future research, serious consideration be given to adoption of the "commission" plan.

Future Tasks for Preventive Medicine

Preventive medicine has long been called the medicine of the future, but what is the future of preventive medicine? I repeat that its future will depend on acceptance, by those who uphold the philosophy of prevention in medicine, of the responsibility for research and the direction it takes and on its willingness to initiate and support vigorous, sustained research in preventive medicine in its literal sense, rather than to leave this to the now-and-then attention of other interests.

A dominant segment of medical research is directed toward the investigation of pathological disturbances which have already become manifest. Clinical attention—and much public health effort—centers on the hope of restoring function or maintaining it at a level that will permit a useful life. Unfortunately, with the exception of certain infectious, toxic, or deficiency diseases, so-called therapeutic procedures do not commonly result in cures, for by the time the manifestations are recognized the defect is well advanced and not ordinarily reversible. This, in general, applies to diabetes, cardiovascular disease, chronic arthritis, cancer, including leukemias, major mental diseases, neurological diseases, pollen sensitizations, and a variety of other disorders. Even with enhanced efforts toward detection of the asymptomatic stages of these disorders, the ultimate result is only slightly influenced.

Progress in our ability to deal with these currently irreversible disorders, or chronic states, calls for increased research, with preventive intent, to study the origins of a disease and the basis of susceptibility to it. It calls for a turn from preautopsy medicine to preclinical medicine. Epidemiologic investigations should be of prime value in identification of susceptible persons and in disclosure of pathogenic factors which convert the susceptible person, the potential case, into a frank case of disease. Beyond this, there is a need to determine the nature of susceptibility, of the defect or injury which depletes the protective reserve, and of the mechanism of the basic injury, to map out the setting. Knowledge should then lead to devising effective procedures of prevention.

Although there are mild stirrings in this direction, preventive medicine is essentially a neglected field. For its fruitful development, active employment of personnel and scientific methodology from all areas of medical science will be needed. In fact, it is an added facet, a necessary supplement to medical research generally. There has been an increase in the wealth of investigative tools with which to reach back into the beginnings of a disorder. But new perspectives, new ideas, and new modes of measurement will be needed. The epidemiologic, clinical, and laboratory disciplines must be merged into an operating philosophy of preventive research. As increased funds have permitted greater freedom of thought and greater boldness in the pursuit of medical research, there has been much wider extension of interest in the origins of these chronic diseases. It probably is evidence also of increasing maturity in research perspectives. Much of this is rising among those engaged in clinical investigation. But my recommendation is that preventive medicine, and especially epidemiology, take a position of forceful leadership in initiation and development in this area. "Grist is ready for the mill, the leaven is active, let's get cooking."

In the September, 1959, issue of the *American Journal of Public Health* there is a series of excellent and frank appraisals of prevention and control of chronic disease. Emphasis is given to the limited facilities now available despite much activity, to the still prevalent emphasis on detection of the disease, to the greater need to understand the problem confronting us, to the need for etiological studies, to the study of susceptible persons, and to a discussion of the information necessary for primary prevention. The total effect is to point out the need for preventive research.

A further and more fundamental product of this research should be the development of adequate standards of health. In seeking information on susceptibility and reserve and protective mechanisms, new biological measurements will have to be developed before early deviations from health and recognition of abnormalities will be detectable. The normal physiological responses to harmful stresses of various kinds will need to be established. The improvement in development and behavior of germ-free animals, despite exposure to varied hazards, is an example of how health may be studied in man. Since much of our present knowledge of health is primitive, the developments in biological science at both the cellular and the molecular level may provide new dimensions for understanding the systemic and "organismal" state. With advancing knowledge a science of health may actually come into being.

This proposal is not intended merely as a declaration of virtuous ideals. Nor would I propose priority for any of the various entities, for in each of the disorders the need for research is great. The determining factor is the imagination and energy of the investigative group. Nevertheless, certain inferences and relationships suggest that atherosclerosis (especially coronary heart disease), diabetes, and rheumatoid arthritis may be more nearly ripe for picking than certain other diseases of a more diversified nature. But cancer and congenital defects are high on the list because of their probable association with infectious agents. It should be emphasized that the field of infection is wide open for study, for there is no adequate information about who, among a group of susceptible persons, will develop frank disease, inapparent infection, or no infection, when all are uniformly exposed, and that prevention of infectious disease is still in its early stages of development.

Report on One Study in Preventive Medicine

The interest evidenced by the School of Public Health at the University of Michigan in the problem of preventive medicine has taken concrete form in the study of one total community—that of Tecumseh, Mich.—with a population of 8,500. The purpose is to study the health and disease and life and death of members of the population in relation to their biological, physical, and social environment. The work was begun as a program undertaken by the faculty of the School of Public Health as a whole, with financial support from the University of Michigan for studies in "human resources." The community was mapped; the population was identified by individual persons, households, and genetic kindreds. Interviews and questionnaires obtained information about any of a series of diseases which the individual subjects and families acknowledged to exist among them. About 50 families gave histories of two or more cases of hypertension or of heart disease, and about 15 told of two cases of diabetes.

Our working hypothesis is as follows: A subject with hypertension or coronary heart disease, for example, serves as an index case. Whether related to environmental exposures encountered in the way or course of life or to genetic factors, the members of the household or of the genetic kindred, or both, are more likely to share those influences than other segments of the population. They are more likely to develop the disorder and hence to provide a focus of susceptible persons. Consistent study of the familial associates should then provide information on susceptibility, the early stages of abnormality, and the course of development of the disease. A developing disease may be observed at different stages in the same unit. Moreover, since persons of all ages are included, observations on contributory factors may be made from early childhood on. That the origins of these diseases go well back into early life seems highly probable. At the kindred level, several generations may be kept under observation. Among those presumed susceptible, pilot studies in the development and evaluation of methods for detection of early aberration can be made. Relationships between the occurrence of different clinical entities can be studied in the same population. The continuing study may also be expected to provide some observations on the incidence of disorders and to suggest features for expanded study in larger populations.

At any rate, with support from the National Heart Institute, examination of the total population has begun, with Dr. Fred Epstein in charge. A comprehensive history, obtained from each family, provides special detail relating to cardiovascular disease, diabetes, arthritis, and chronic pulmonary disease. Each family is then examined clinically—a thorough examination being made, with supportive laboratory studies and again with special emphasis on cardiovascular disease. The population is examined in representative aliquots. In this undertaking we have had the warm support and assistance of the staff of the clinical departments, especially the medical staff, but including surgeons and psychiatrists. A special dental examination is being made of one sample of subjects. Surveys of spastic deformities, fertility, and respiratory disease by family distribution are being made. To date, nearly one-third of the population has had its examination, as requested, with an acceptance of 90 to 92%. The data are being edited and recorded, and certain preliminary measures of uniformity have been made. Although no analyses have been made as yet, it is quite clear that interesting findings will be obtained. With establishment of the prevalence and selective distribution of various diseases by means of a thorough medical history and examination, the identification of the population will have been completed, and the foundations will have been laid for intensive continued study of special segments that harbor a given disorder or groups of diseases.

Summary

New dimensions and postures are recommended for medical research. The guiding concepts should be (1) that research in preventive medicine in the literal sense be forcefully established, strongly supported, and effectively maintained; (2) that research in infectious diseases not be dissipated by deceiving slogans; (3) that research move toward prevention of the so-called chronic diseases whose scope is increasing; and (4) that preventive medicine will be the medicine of the future only if it accepts its proper responsibility, for the future is very near.

Our views of health, and its values, must, like our educational system, reflect our culture and our way of life. They must be projected as the image of our ideals. Freedom and democracy may seem like hollow triumphs if the hopes of life are submerged in a welter of disease. Security and longer life can be miserable acquisitions, if they mean only the continuation of unhealthy states. Preventive medicine can be our most progressive demonstration to all the world of our belief in human life and happiness. Peace, health, and security are of the same fabric. We should weave more of it.

DIABETES MELLITUS IN AN EMPLOYED POPULATION

Sidney Pell, Ph.D.
and
C. A. D'Alonzo, M.D., Wilmington, Del.

Medical information on 90,596 employees of a large company was surveyed during 1956 and 1957 in an appraisal of facts regarding diabetes. The company physicians reported on 408 employees having the disease and an equal number of nondiabetic employees matching the diabetic group as to age, sex, occupation, and location. The incidence of diabetes was 4.5 per 1,000 employees, 4.8 for men (370) and 2.7 for women (38). No significant difference was found in the distribution of ABO blood groups between diabetics and nondiabetics. Although obesity was more common to the diabetics, 92.1% of them had been able to lose weight since the discovery of their diabetes. Hypertension occurred more frequently in the employees with diabetes, especially those overweight, but obesity could not be singled out as the main cause of the hypertension.

Series of cases for diabetic studies are usually drawn from clinics or hospitals; less frequently from the population at large. Generalizations of findings from the former sources are somewhat limited because their patients tend to represent specific ethnic and socioeconomic groups, and the treatment they receive is standardized in accordance with the general philosophy of diabetic management adopted by the physician in charge. Population studies have the advantage of encompassing a wider representation of the diabetic population, but they also have the disadvantages of being costly and lacking in extensive and detailed medical histories.

The diabetics who comprise the subject matter of this paper are employees of E. I. du Pont de Nemours & Company. One might consider them a sample of a third group available for study; that is, the employed diabetic. Although our diabetics are a select group, in that they may be healthier and better controlled than diabetics in general, they are a fruitful source of material for several reasons. First, they provide an opportunity to study the effect of the disease on their status as employees. Second, the patients come from all parts of the country. Third, they represent a large variety of occupations and a wide range of economic levels. Fourth, many clinical and laboratory data are available from records of periodic health examinations. And, finally, it is a simple matter to obtain a randomly drawn control group, matched to the diabetics by age, sex, occupation, and geographical area.

The findings reported here deal with the prevalence of diabetes in the company, variations in prevalence by job levels, the relation of the disease to ABO blood groups, and an analysis of the occurrence of complications and associated diseases. Articles concerning genetic factors and the experience of our diabetics with respect to sickness, absenteeism, and frequency of injuries will be published in subsequent papers.

Source of Material and Survey Procedures

Company Medical Facilities, Policies, and Records.—During the past 25 years, it has been the practice of the company to provide an extensive periodic physical examination to all employees. These examinations are given, in almost all instances, by company physicians. The laboratory tests include hemoglobin determinations, whit blood cell counts, and urinalyses to test for th presence of sugar and albumin. More intensiv blood and urine studies are performed when indicated by laboratory findings and history. The routine examination also includes a chest x-ray and for employees past 35 years of age, at least on electrocardiogram.

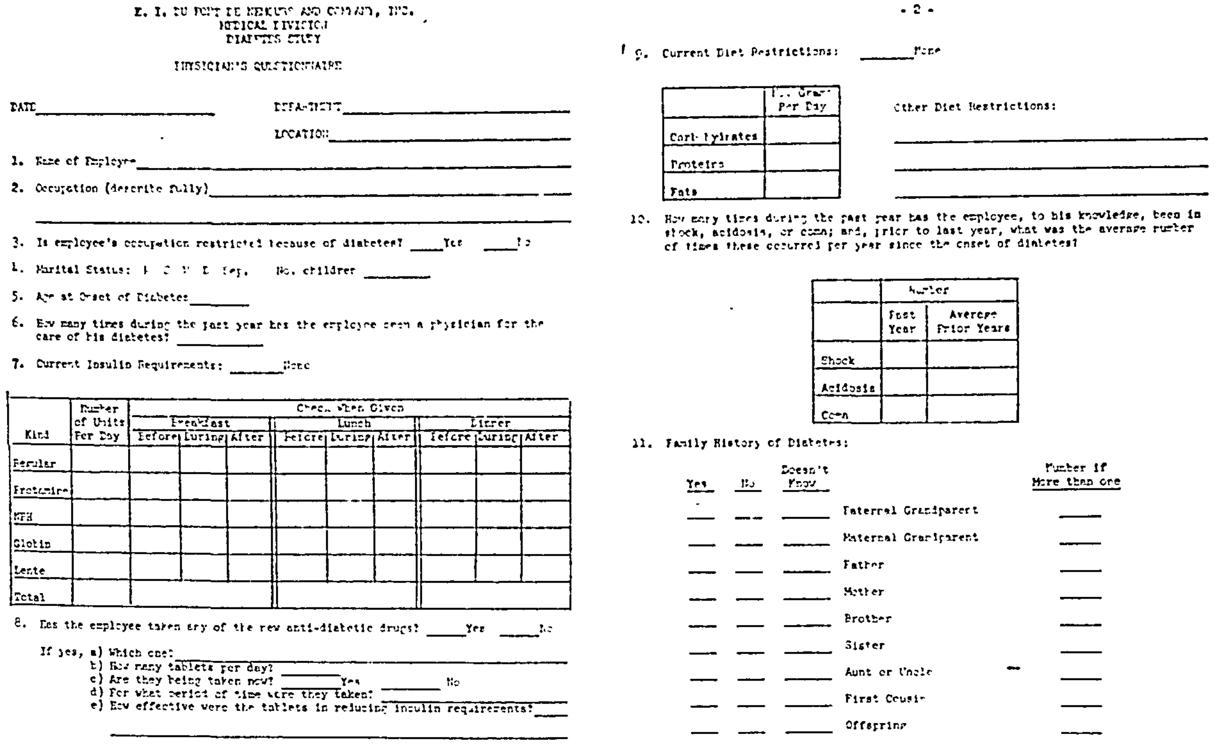
Almost all employees have been receiving thei medical examinations once a year, but many ar seen more frequently for consultations and specia examinations to detect early any possible advers effects of potential occupational hazards, as part o our preventive medical program. In addition, production employees who are absent for reason o illness or injury must report to the plant medica unit for evaluation on their return to work.

When an employee exhibits abnormal condition that require treatment or further diagnostic measures, he is referred to his family physician or specialist. Contact between the company and th local medical community is maintained, to follow the progress of patients. This contact is also o value in the administration of the company sicknes benefit plans, which require the attending physician to certify the fact and cause of disability.

Biostatistician (Dr. Pell) and Assistant Medical Director, Medical Division (Dr. D'Alonzo), E. I. du Pont de Nemours and Company, Inc.

Employees with glycosuria are given blood sugar (usually postprandial) or glucose-tolerance tests. Most company installations have facilities to administer these tests, but those which do not have the work done at a local laboratory. Some company physicians have blood sugar determinations made when there is a family history of diabetes without glycosuria. All employees suspected of having diabetes are examined closely until a diagnosis of diabetes is clearly established or eliminated.

The company does not, as a matter of policy, refuse employment to anyone because of diabetes mellitus, except when the applicant cannot demonstrate that he is able to control the disease. The suggested policy and procedure for company physicians is stated as follows: "Uncontrolled diabetes is a severe hazard. These cases should not be accepted, under any circumstances, until the blood sugar is within normal limits and medically controlled. If the applicant is accepted, he should be followed up every three months or so, or at least until the examiner satisfies himself that the diabetes is well managed."[1] Diabetic employees are encouraged to seek the help and advice of their personal physicians and their company physicians for problems concerning the management of their diabetes in relation to their job.



E. I. DU PONT DE NEMOURS AND COMPANY, INC.
MEDICAL DIVISION
DIABETES STUDY

PHYSICIAN'S QUESTIONNAIRE

DATE ____ DEPARTMENT ____

LOCATION ____

1. Name of Employee ____

2. Occupation (describe fully) ____

3. Is employee's occupation restricted because of diabetes? ____Yes ____No

4. Marital Status: M S W D Sep. No. children ____

5. Age at Onset of Diabetes ____

6. How many times during the past year has the employee seen a physician for the care of his diabetes? ____

7. Current Insulin Requirements: ____None

Kind	Number of Units Per Day	Check When Given								
		Breakfast			Lunch			Dinner		
		Before	During	After	Before	During	After	Before	During	After
Regular										
Protamine										
NPH										
Globin										
Lente										
Total										

8. Has the employee taken any of the new anti-diabetic drugs? ____Yes ____No

If yes, a) Which one? ____
b) How many tablets per day? ____
c) Are they being taken now? ____Yes ____No
d) For what period of time were they taken? ____
e) How effective were the tablets in reducing insulin requirements? ____

- 2 -

9. Current Diet Restrictions: ____None

	No. Grams Per Day
Carbohydrates	
Proteins	
Fats	

Other Diet Restrictions:

10. How many times during the past year has the employee, to his knowledge, been in shock, acidosis, or coma; and, prior to last year, what was the average number of times these occurred per year since the onset of diabetes?

	Number	
	Past Year	Average Prior Years
Shock		
Acidosis		
Coma		

11. Family History of Diabetes:

Yes	No	Doesn't Know		Number if More than one
____	____	____	Paternal Grandparent	____
____	____	____	Maternal Grandparent	____
____	____	____	Father	____
____	____	____	Mother	____
____	____	____	Brother	____
____	____	____	Sister	____
____	____	____	Aunt or Uncle	____
____	____	____	First Cousin	____
____	____	____	Offspring	____

Questionnaire distributed to company physicians for assistance in interviewing diabetics.

Survey Procedures.—Our survey was begun in June, 1956. At that time, we distributed questionnaires (see figure) to all company physicians and asked them to complete the questionnaire by interviewing every diabetic in their plant. Thus, the company physician was given the responsibility of identifying the diabetic. Since each doctor is assigned about 1,000 employees, the names of the few diabetics seen by them could easily be recalled or obtained from their medical records. Nevertheless, we allowed a little more than a year to elapse for the completion of the questionnaire. During that time, each physician examined all of his patients at least once and was in a position to identify diabetics not recalled by him at the start of the survey.

The choice of diagnostic criteria was left, of course, to the judgment of the employee's personal physician. In questionable cases, we recommended to the company physician that, for purposes of this study, a diagnosis of diabetes be made when the blood sugar level exceeded 170 mg. per 100 cc. in one-half to one hour after the ingestion of a test meal (or a meal high in carbohydrates) or when the blood sugar level did not return to a level below 150 mg. per 100 cc. two hours after the meal, or both of these conditions obtained. Of course, no set of criteria will prevent false-negative and false-positive diagnoses. In our company, however, these risks are reduced because of the repeated health examinations and close follow-up of patients with borderline and indeterminate cases.

After obtaining the names of all the known diabetics in the company, we selected a control employee, matched to each diabetic by age (five-year categories), sex, occupation (i. e., production or salaried), and location. The controls were selected by means of random numbers from a complete listing of company employees. We then requested the medical records of the diabetics and controls to make abstracts of information pertinent to our study.

Prevalence of Diabetes

Variation by Age and Sex.—During the one-year period in which the survey was conducted (June, 1956, to June, 1957), company physicians reported 408 patients with diabetes among the company's 90,596 employees, a prevalence rate of 4.5 per 1,000 persons. Among these were 370 men and 38 women. Prevalence rates by age and sex, shown in table 1, indicate the well-known increase in prevalence with age.

TABLE 1.—*Prevalence of Diabetes Mellitus by Age and Sex**

	All Employees		Men		Women	
Age, Yr.	No.	Rate	No.	Rate	No.	Rate
<20	1	1.3	1	2.8	0	0
20-24	1	0.1	0	0	1	0.4
25-29	8	0.6	8	0.7	0	0
30-34	29	1.9	26	2.0	3	1.3
35-39	50	3.4	47	3.7	3	1.5
40-44	56	4.3	52	4.6	4	2.7
45-49	54	5.1	50	5.3	4	3.1
50-54	76	10.2	68	10.3	8	9.4
55-59	68	14.7	60	14.5	8	15.7
60-64	65	21.3	58	21.0	7	23.8
Total	408	4.5	370	4.8	38	2.7

* Rates per 1,000.

Comparisons with Other Surveys.—The actual number of diabetics in the United States has been a matter of speculation for many years. The National Health Survey of 1935-1936[2] obtained a prevalence rate of 3.7 per 1,000 by means of household interviews. That this figure is a gross underestimate of the actual prevalence of diabetes has been strongly suggested by more recent population surveys in which blood sugar tests have been used as a basis for the identification of diabetics. In Oxford, Mass., the prevalence rate was found to be 20 per 1,000,[3] and in three communities in Ontario, Canada, 12.9 per 1,000.[4] Among industrial surveys, prevalence rates per 1,000 were reported as 5.5 by Hemmett,[5] 13.0 by Wade,[6] and 16.0 by Canelo and others.[7]

If the screening surveys that have been cited come closest to estimating the actual prevalence of diabetes in the general population, the observed rate in our company, 4.5 per 1,000, must be considered low. Two possible explanations for the difference are as follows.

Screening Methods.—Most company medical units rely only on the presence of glycosuria as a means of identifying potential diabetics. Wilkerson and co-workers[8] demonstrated that urine tests alone are nonspecific and insensitive for screening purposes. Although the annual repetition of urinalyses done on company employees increases the chances of detecting diabetes, it is possible that some mild cases remain unidentified.

Selectivity of Company Population.—As stated earlier, company policy does not favor the employment of severe uncontrolled diabetics. In addition to this group, there may be other diabetics who do not enter the company population. These may include diabetics with disabling complications, or those, who, because of their condition, do not seek employment with the company.

Variation in Prevalence by Job Level

Male employees were divided into five broad occupational categories. One category consists of production workers; that is, craftsmen, operatives, and other employees engaged in various types of skilled, semiskilled, and unskilled manual labor. This group comprises about two-thirds of the male population in the company. The other four categories consist of salaried employees grouped according to their income level. The highest group is made up of persons in managerial and executive positions, while the other levels include supervisory, professional, technical, and clerical personnel.

Age-adjusted prevalence rates in each of the five categories are shown in table 2. Differences among these rates are significant ($0.05 > p > 0.02$). Among the four salaried groups, there can be seen an inverse relationship between job level and prevalence of diabetes. This association may be due to a selective mechanism, by which diabetics may have, for various reasons, less chance than nondiabetics for promotion to supervisory and managerial positions.

The prevalence rate among production employees is lower than that found in the two lower categories of salaried employees. Part of this difference may be explained by the sedentary nature of the work done by salaried personnel or, conversely, the protective effect of the physical activity of production workers. Another factor may be a tendency of some diabetics to move or keep away from occupations in production areas because of the demands of shift work.

TABLE 2.—*Age-Adjusted Prevalence Rates of Diabetes Mellitus Among Men, by Job Level*

Job Level	Employee Population	Diabetics, No.	Age-adjusted Rate per 1,000
Salaried: lowest	5,072	31	6.3
Salaried: lower middle	10,014	51	5.6
Production	51,279	233	4.7
Salaried: upper middle	9,118	49	4.6
Salaried: highest	970	6	3.5
Total	76,153	370	4.8

It is interesting that the pattern of occupational variation in prevalence of diabetes, described above, is similar to the pattern we found in studying the incidence of acute myocardial infarction. The rankings of the five job categories were identical in the two studies. It is possible that the incidence or prevalence of other forms of chronic disease may yield similar occupational differences and that the same factors may be operating to produce them.

Use of Orally Given Hypoglycemic Agents

During the one-year period of our survey, only nine patients reported the use of orally given drugs to control the blood sugar level. Five of these patients, who normally require a daily insulin dosage of 26 units or more, had to resume taking insulin because the drugs were not effective. The drugs appeared to be successful for the other four diabetics, but three of them had never taken insulin, and the other had taken only 15 units per day.

Blood Types

Some company installations include blood typing as a part of the preemployment medical examination. Among the subjects in this study, we were able to obtain the ABO blood groupings of 265 diabetics and 275 controls (table 3). Differences in the frequency distributions of the blood types between the diabetics and controls are small and can easily be attributed to sampling variation ($p > 0.50$). Our findings are not in agreement with those of McConnell and associates,[10] who reported an increased frequency of persons with group A and a decreased frequency of those with group O blood among 1,333 diabetics who were compared to controls.

Overweight and Hypertension

Criteria.—To classify our subjects according to the presence or absence of overweight and hypertension, we used, for this and other studies we are undertaking, the following criteria.

A person was classified as overweight if his body weight, as measured during his latest periodic health examination, exceeded his ideal weight by 20% or more. We specified a person's ideal weight as the weight midway between the allowable extremes for a person of medium frame, as recommended in the height-and-weight tables of the Metropolitan Life Insurance Company.

TABLE 3.—*Distribution of Blood Types Among Diabetics and Controls*

Blood Type	Diabetics No.	Diabetics %	Controls No.	Controls %
O	131	49.4	132	48.0
A	93	35.1	102	37.1
B	27	10.2	32	11.6
AB	14	5.3	9	3.3
Subtotal	265		275	
Unknown	143		133	
Total	408	100.0	408	100.0

A classification of hypertension was made on the basis of blood pressure readings that were taken during the past 10 years at the time of the employee's periodic health examination. He was designated as hypertensive if his records showed two successive annual readings of 150 mm. Hg or more systolic or 94 mm. Hg or more diastolic.

Frequency of Occurrence.—Excess weight in diabetics is a common clinical finding, and its positive role in the etiology of the disease is well known. In our series, 36.0% of the diabetics are currently overweight, but, of 349 diabetics for whom information is available, 164, or 47.0%, were overweight at the time of onset of the diabetes. These figures are contrasted to 27.4%, the proportion of the controls who are overweight at the present time. The success of our overweight diabetics in losing weight is indicated by the fact that, of the 164 diabetics who were overweight at onset, 151, or 92.1%, have shown a net loss in weight since that time.

TABLE 4.—*Prevalence of Hypertension Among Diabetics and Controls by Percentage Overweight*

Weight Variation, %	Diabetics Total, No.	Diabetics Hypertensives No	Diabetics Hypertensives %	Controls Total, No.	Controls Hypertensives No.	Controls Hypertensives %
Underweight	91	4	4.4	96	6	6.3
Overweight						
<10	88	7	8.0	81	8	9.9
10-19	80	12	15.0	118	11	9.3
20-29	73	16	21.9	64	7	10.9
>29	73	23	31.5	47	12	25.5
Total	405	62	15.3	406	44	10.8
Unknown	3	1		2	0	
Grand Total	408	63	15.4	408	44	10.8

Several investigators [11] have reported that hypertension occurs more frequently in diabetics than in nondiabetics. Munro and colleagues [11b] found the difference to be much more pronounced in women than in men. According to our criteria, described above, hypertension is present in 63 diabetics and 44 controls, or 15.4% and 10.8%, respectively, of the total in each group ($p = 0.06$). Overweight and hypertension occur jointly in 9.6% of the diabetics and 4.7% of the controls; that is, about twice as frequently in the diabetic group ($p < 0.01$).

Since overweight is more common among diabetics than nondiabetics, and since there is a positive association between overweight and hypertension, one might suspect that the higher frequency of hypertension among diabetics might be due to the higher frequency of overweight among them. Our data, however, indicate that the excess of hypertension among diabetics cannot be attributed to excess body weight alone. As seen in table 4, the greater prevalence of hypertension among diabetics occurs in each of the three highest categories of overweight. Data obtained by Munro and colleagues [11b] led them to the same conclusion.

Relation to Severity of Diabetes.—The prevalence of hypertension by daily insulin dosage, as shown in table 5, indicates an inverse association between these two variables. Of 236 diabetics who take no insulin or less than 20 units per day, 48, or about

20%, are hypertensive. The prevalence of hypertension decreases in each successive category of daily insulin dosage. Among the most severe cases, that is, in patients requiring 50 or more units per day, hypertension is present in only 3 of 52 diabetics, or 5.8%. Although the number of hypertensives in each category is small, the probability that the differences among the prevalence rates will occur by chance alone is about 0.02.

Table 5.—*Prevalence of Hypertension by Daily Insulin Dosage*

Daily Insulin Dosage, Units	Total	Hypertensive	
		No.	%
None	194	38	19.6
1-19	43	10	23.3
20-29	39	5	12.8
30-49	78	7	9.0
>49	52	3	5.8
Total	406	63	15.4

To explore this matter further, we compared the prevalence of hypertension among diabetics with that of the controls by the presence or absence of overweight and divided the diabetics into two groups: those who took no insulin or less than 20 units per day (mild cases) and those who took 20 or more units per day (moderate and severe cases).

The data, presented in table 6, show no significant differences in prevalence of hypertension between controls and moderate and severe diabetics. This is true for persons who are overweight as well as those who are not overweight. Among persons who are not overweight, there are no significant differences in prevalence of hypertension among mild diabetics, moderate and severe diabetics, and nondiabetic controls.

Among overweight persons, however, the prevalence of hypertension is significantly greater among the mild diabetics than it is among the moderate and severe diabetics and the controls ($p<0.05$). Among the 110 overweight diabetics with mild disease, hypertension is present in 30.9%. This is contrasted to 13.9% in the moderate and severe group and 17.1% in the control group.

Table 6.—*Prevalence of Hypertension by Presence or Absence of Overweight Among Controls and Among Diabetics According to Daily Insulin Dosage*

	Mild Diabetics—No Insulin or Less than 20 Units			Moderate and Severe Diabetics—20 or more Units			Controls		
		Hypertensive			Hypertensive			Hypertensive	
	Total	No.	%	Total	No.	%	Total	No.	%
Not overweight	126	13	10.3	133	10	7.5	295	25	8.5
Overweight	110	34	30.9	36	5	13.9	111	19	17.1
Total	236	47	19.9	169	15	8.9	406	44	10.8

Thus, the higher rate of hypertension found in our series of diabetics, when compared to the controls, is concentrated in the overweight patients with mild cases.

Diseases Associated with Diabetes

Table 7 shows the frequency with which the occurrence of certain diseases was noted in the medical records of the diabetics and controls. In assessing the differences between the two groups, consideration should be given to these factors. First, for some diseases listed there are not a sufficient number of cases with which to obtain a reliable estimate of the true difference between the two groups. Second, some of the diseases may be present but not diagnosed, and, if diagnosed, inadvertently omitted from the medical record. Third, diabetics are seen by physicians more frequently than are nondiabetics; hence, the presence of a disease is more likely to be detected earlier in a diabetic than in a nondiabetic. The biases just mentioned are probably minimized in our series because of the thoroughness of the periodic health examination provided by the company to both diabetics and nondiabetics.

Table 7.—*History of Certain Diseases Among Diabetics and Controls*

	Diabetics		Controls		
	No.	%	No.	%	p*
Hypertension	63	15.4	44	10.8	.06
Coronary artery disease	32	7.8	11	2.7	<.01
Skin disease	30	7.4	20	4.9	>.10
Gallbladder disease	20	4.9	8	2.0	<.05
Peripheral vascular disease	11	2.7	2	0.5	<.05
Retinitis	10	2.5	0	0	<.01
Neuropathy	9	2.2	5	1.2	>.30
Cataracts	5	1.2	8	2.0	>.50
Thyroid disturbance	8	2.0	9	2.2	>.20
Peptic ulcer	12	2.9	24	5.9	<.05

* Probability of difference between diabetics and controls occurring by chance alone.

A higher prevalence rate among diabetics, greater than would be expected by chance alone ($p<0.05$), was found to occur in the cases of coronary artery disease, gallbladder disease, peripheral vascular disease, and retinitis. The proneness of diabetics to develop these diseases is well known. Skin diseases were also more common among the diabetics than the nondiabetics in our study, but the difference in prevalence rates is not great enough to exclude the possibility that it arose by chance alone. Data on neuropathies, cataracts, and thyroid diseases are too fragmentary to draw inferences from them. The relation of hypertension to diabetes was discussed in the preceding section.

Of particular interest is the more frequent occurrence of peptic ulceration among the nondiabetics; i. e., 5.9% compared to 2.9% in the diabetic group ($p<0.05$). This is consistent with the findings of other studies. Rothenberg and Teicher[12] reported peptic ulcer in 0.25% of 3,525 diabetics compared to 1.49% of 130,500 total hospital admissions. At the Mayo Clinic,[13] peptic ulcer was found in 2.3% of 2,584 diabetics and in 3.7% of the total number of admissions. One might suspect that age differences between the diabetics and nondiabetics in these studies might account for the lower prevalence of peptic ulceration among the diabetics, because diabetes is prevalent in older persons and peptic ulcer in younger persons. In our study, however, the nondiabetic controls were matched to the diabetics by age, so that this factor cannot explain the difference we observed.

Comment

That some relationship exists between the pituitary gland and diabetes mellitus has been well established by the work of Houssay.[14] He demonstrated experimentally a marked reduction of the severity of diabetes in animals by removal of the anterior pituitary gland, and, conversely, the production of diabetic symptoms by the administration of anterior pituitary extract. Clinical indications of this relationship are the rapid growth and early maturity of diabetic children and the occurrence of glycosuria in such conditions as pregnancy, basophilic adenomas of the pituitary gland, and as a sequela in the clinical use of ACTH.

Since hormones are implicated in the etiology of diabetes mellitus, it is possible that hormonal disturbances may play a part in the development of certain "stress diseases" among diabetics. In our series of cases, the prevalence of essential hypertension, commonly regarded as a stress disease, was found to be excessively high among the overweight diabetics with mild disease and inversely related to insulin dosage. These findings bring to mind certain interesting speculations. For example, does insulin, itself have a blocking, inhibitory, or neutralizing effect on the pituitary-adrenal axis? One might also consider, in this regard, the homeostatic action of insulin and epinephrine in the maintenance of normal blood sugar levels. A high intake of insulin may be accompanied by a reduced output of epinephrine, thus tending to lower blood pressure levels, whereas the diabetics who take little or no insulin may have a relatively high output of epinephrine, and, consequently, higher blood pressures.

Although stress may be involved as a component in the etiology of such conditions as obesity, hypertension, atherosclerosis, and cholelithiasis, the excess prevalence of these diseases among diabetics may be due, partly or wholly, to the derangement of carbohydrate and lipid metabolism characteristic of diabetes.

Peptic ulcer is the one stress disease which has been found to be less common among diabetics than nondiabetics. This is not consistent with the idea that diabetes and complicating stress diseases have a common origin in the stress mechanism, but there are possible explanations for this apparent contradiction. First, the body's response to stress is not necessarily mediated through the gastric area, but may operate via the pancreatic-adrenal route alone or through more than one pathway. Second, Clarke[15] has suggested that the amount of secretion of hydrochloric acid may be determined by a genetic factor transmitted with the ABO blood type, O leading to hyperchlorhydria and A to achlorhydria. In support of this view, he cited the increased frequency of type O blood among persons who have peptic ulcer, which is associated with hyperchlorhydria, and the excess of type A among persons with gastric carcinoma and pernicious anemia, diseases associated with achlorhydria. He then cited a study by McConnell which showed increased frequency of group A among young diabetics, pointing out that in persons with diabetes mellitus duodenal ulcer is rare and achlorhydria common. Thus, under Clarke's hypothesis, the decreased prevalence of peptic ulcer among diabetics would be due to the protection afforded by a genetically transmitted achlorhydria.

Summary

A survey of diabetics employed by E. I. du Pont de Nemours & Company revealed 408 cases, a prevalence rate of 4.5 per 1,000 persons. Among salaried employees, prevalence was inversely related to job level. The disease was found to be less prevalent among production workers than among the lower level salaried employees. No significant difference was found in the distribution of ABO blood groups between the diabetics and the controls. Overweight was found to be more prevalent among the diabetics than the controls, but 92.1% of the diabetics who were overweight at the time of onset have shown a net loss in weight since that time. Hypertension was more common among the diabetics than the controls, but the excess was found to be concentrated in the overweight patients with mild cases. The higher prevalence of hypertension among the diabetics was not due to the higher prevalence of overweight among them.

The prevalence of hypertension was inversely related to daily insulin dosage. There are possible explanations for this relationship. The prevalence of coronary artery disease, gallbladder disease, peripheral vascular disease, and retinitis was significantly greater among the diabetics than the controls. The proneness of diabetics to these diseases has been generally accepted on the basis of several postmortem studies, clinical observations, and the relation of these diseases to the pathology of diabetes. A history of peptic ulcer was significantly more common among the nondiabetic controls than the diabetics, confirming the findings of other studies.

Dr. A. J. Fleming and Mrs. Sara M. Rodgers assisted in the preparation of this study.

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NONUNION OF THE CLAVICLE

Charles S. Neer II, M.D., New York

Ununited fractures of the clavicle are rare, and when nonunion occurs the cause should be found. Of 18 cases of nonunion here studied, 4 were in the lateral third of the bone, and nonunion was explained by the rupture of the coracoclavicular ligament. When this ligament is intact, union is generally prompt. The other 14 were in the middle third of the bone, and in 10 of these nonunion was ascribed to local tissue damage, stripping of soft parts, loss of valuable bone, inadequate internal fixation, and infection connected with the initial treatment by open operation. Surgical correction of fractures of the middle third must be done with due regard to fixation and with minimal damage to soft parts. Fractures of the lateral third, if complicated by disruption of the acromioclavicular ligament, are best treated by internal fixation.

The clavicle, as a bone, is a nonconformist. It is the first to ossify in the embryo, and it continues throughout life to enjoy a remarkable reputation for its ability to form bone and heal. One of every 20 fractures[1] occurs in the clavicle, and yet failure of union has rarely been recognized. Nevertheless, during the past year, five patients with ununited fractures of this "invincible bone" were seen at the New York Orthopaedic-Columbia-Presbyterian Medical Center. It has recently been suggested[2] that the incidence of this complication is rising. These facts prompted a study of the causal factors, pathology, and treatment of this condition.

Materials and Methods

Table 1 shows an analysis of 18 ununited fractures of the clavicle in patients treated by our service between the years 1936 and 1959. Patients with pseudarthroses secondary to neoplastic, congenital, or metabolic processes were excluded; only those with traumatic lesions were considered. Two with acute fractures that had been initially excised were omitted because both the cause and the pathological findings were atypical. Three children with ununited clavicles were thought to have complications of birth fractures rather than failure of development.[3] They were excluded from the series; how-

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From the Department of Orthopædic Surgery, College of Physicians and Surgeons, Columbia University, and the Fracture Service, New York Orthopædic Hospital, Columbia-Presbyterian Medical Center.

Read before the Section on Orthopedic Surgery at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

ever, they are of interest and will be described briefly later. With the exception of case 18, the progress of these patients was followed clinically and roentgenologically for a minimum of 6 months, with an average follow-up period of 20 months.

Cause.—Lesions of the middle and outer thirds should be considered separately. No ununited fractures of the inner third were seen. All four of the patients with pseudarthroses in the outer third also had tears of the coracoclavicular ligaments (fig. 1). When these ligaments were intact, prompt union was the rule. When they were disrupted, delayed union or nonunion followed, unless the fracture was stabilized by internal fixation. The ligamentous disruption must be looked on as the factor responsible for nonunion in the outer third.

Fractures are more common in the middle third (67%), and, as expected, most complications, including nonunion, occurred in patients with fractures in this region. Of the 14 patients with ununited midclavicular lesions in this series, 10 had been treated initially by open operation (table 2). It is interesting that of 2,235 patients with middle-third fractures treated by closed methods in our clinic, only 3 (0.1%) had failure of union. On the other hand, of 45 patients treated by immediate open reduction, 2 (4.6%) had failure of bone union. These facts indicate that the most important causal factor in nonunion of fractures of the middle third has been improper open surgery. Local tissue damage, soft part stripping, removal of valuable bone, inadequate internal fixation, and infection were frequent features of these operative procedures. Local tissue damage had often been augmented by a severe initial injury. Other causal factors included inadequate immobilization of the unconscious patient and, in two instances, rotation of the intermediate fragment, with interposition of

TABLE 1.—*Analysis of Eighteen Patients with Nonunion of Clavicle*

Case No.	Year	Patient Data*	Injury: Condition	Injury: Type and Duration	Injury: Cause	Injury: Symptoms	Initial Treatment	Repair	Result
1	1936	M, 20, truck-driver	3rd refracture	Type 1, right one-third, 4 yr	Underdeveloped clavicle	Deformity	Closed	Refused	Full heavy use, no pain
2	1940	M, 23, laborer	Accident while intoxicated	Type 1, broken wire, middle one-third, right, 2 yr	Operation	None	Open	Refused	Full heavy use, no pain
3	1940	M, 49, steel worker	Hit by 400-lb. beam	Type 1, left middle one-third, 3 yr	Severe injury, operation	Pain, weakness	Open	Tibial graft, IM rod, wire loop, spica	Good
4	1941	M, 22, roofer	14-ft. fall	Type 1, left middle one-third, 11 mo.	Severe injury, rotated fragment	Pain	Closed	Local chips, IM rod, wire loop, spica	Good
5	1945	M, 17, student	Automobile accident	Type 2, ossified ligaments, outer left one-third, 10 mo.	Torn coraco-clavicular	Pain	Closed	Local chips, plate, spica	Good
6	1945	M, 42, executive	Fall from bicycle	Type 2, left middle one-third, 22 mo.	Operation	Weakness	Open	Refused	Full office work, no pain
7	1947	F, 13, student	Acrobatics	Type 1, broken wire, right middle one-third, 1 yr.	Operation	Pain, deformity	Open	Local chips, 2 wire loops, spica	Good
8	1948	M, 46, florist	Fall from step-ladder	Type 1, right outer one-third, 7 mo.	Torn coraco-clavicular	Pain	Open	Refused	Working 4½ yrs. later, wires broken
9	1949	M, 30, executive	Fall from horse	Type 2, resorption, adherent subclavian, right, 4 yr.	Operation	Weakness, Pain	Open	Iliac graft, rush nail, spica	Good
10	1951	F, 30, housewife	Fall	Type 1, broken wire, left middle one-third, 11 yr.	Operation	Deformity, weakness	Open	Removal of bone prominence and wire	Poor
11	1954	F, 58, housewife	20-ft. fall	Type 1, ossified ligaments, left outer one-third, 2 yr.	Torn coraco-clavicular	Pain, fatigue	None, multiple injuries	Refused	Persistent symptoms
12	1956	F, 18, student	Surgical approach	Type 2, resorption, right middle one-third, 3 yr.	Operation	Deformity, fatigue	Open	Tibial graft, IM rod, spica	Poor
13	1957	M, 40, executive	Surgical approach	Type 2, infection, resorption, right middle one-third, 18 mo.	Operation	Pain	Open	Tibial graft, screws, rod, loop, spica	Poor
14	1958	F, 35, housewife	Fall	Type 2, resorption, left middle one-third, 13 mo.	Operation, infection	Pain	Open	Iliac graft, IM rod, spica	Poor
15	1958	M, 58, taxicab driver	Automobile accident	Type 1, right middle one-third, 9 mo.	Severe trauma, rotated fragment, coma	Click, weakness	None, multiple injuries	Refused	Full use as cabdriver
16	1958	F, 50, housewife	Fall from horse	Type 2, resorption, right middle one-third, 1 yr.	Operation, infection	Pain, deformity	Open	Iliac graft, IM rod, loop, spica	Good
17	1958	M, 33, executive	Fall from horse	Type 1, ossified ligaments, right outer one-third, 10 mo.	Torn coraco-clavicular ligaments	Tenderness, occasional pain	Closed	Refused	Pain with tennis and golf
18	1959	F, 44, housewife	Automobile accident	Type 2, right middle one-third, 8 mo.	Operation	Pain	Open	Frozen homoplastic graft, IM rod, spica	Inadequate follow-up examination

* Sex, age, and occupation.

Nonunion of the Clavicle in Children.—Defects in children should be considered separately, because it is impossible to differentiate positively between congenital pseudarthrosis due to failure of development and traumatic defect. Three children under 12 years of age were seen who were thought to have ununited birth fractures. In each, the lesion was unilateral and had been noted for the first time when the child was 2 to 3 months of age, and the "tumor" increased in size as the child grew older. Roentgenography indicated middle third defects with ample bone substance and a false joint (fig. 7). There were no associated congenital anomalies elsewhere in the body. Repair was easily accomplished because there was adequate length. The embryologist[6] and radiologist[7] at our center believed that these lesions had the characteristics of ununited fractures rather than developmental defects. It therefore seems probable that they should be differentiated from neurofibromatosis or failure of development, especially because their prognosis after repair is so much better.

Comment

Open reduction and internal fixation constitute the preferred procedure in a few specific patients with clavicular fractures, e. g., those with fractures of the outer third associated with tears of the coracoclavicular ligaments, middle third fractures with rotation of a large intermediate fragment, soft tissue interposition, or vascular or brachial plexus compression. Operative treatment may also be necessary for immobilization in certain patients with

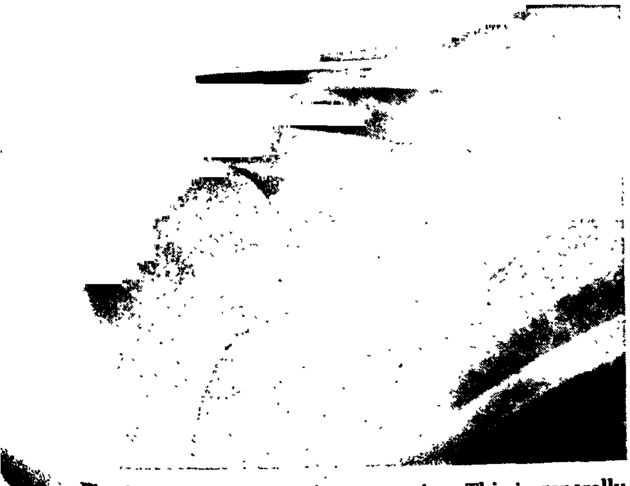

Fig. 6.—Repair of outer [illegible] nonunion. This is generally accomplished by [illegible] bone union.

Summary and Conclusions

A series of 18 patients with ununited fractures of the clavicle is presented. Four fractures were in the outer third and 14 were in the middle third. The clavicle is not "invincible." Lack of immobilization, as in comatose patients, may result in nonunion. Delayed union or nonunion of fractures of the outer third is produced by the instability associated with tears of the coracoclavicular ligaments. Outer third fractures with concomitant ligamentous disruption are best treated by internal fixation, in distinction to fractures in which the ligaments are intact. By far the most frequent cause of nonunion of fractures in the middle third has been improper initial operation. Operation here must be done with the same regard for soft part attachments and fixation as in other open reductions.

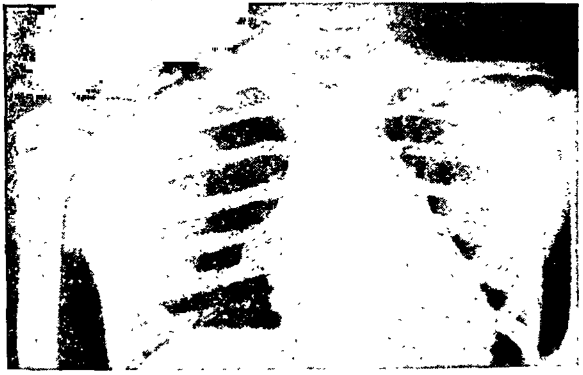

Fig. 7.—Probable nonunion of birth fracture. Although it is impossible to differentiate this from pseudarthrosis due to defective development, it seems probable that certain of these lesions, such as one shown, are actually ununited birth fractures.

Nonunion of the clavicle usually produces sufficient deformity and symptoms to require treatment. Treatment should consist of the reestablishment of bone continuity rather than excision, except when the lesion is producing pressure on the brachial plexus or subclavian vessels or in pathological fractures in patients whose life expectancy is limited. Bone union is more apt to occur if end-to-end contact of the fragments is maintained rather than the gaps bridged with bone grafts.

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POSTPARTUM HYPERTENSION AFTER USE OF VASOCONSTRICTOR AND OXYTOCIC DRUGS

ETIOLOGY, INCIDENCE, COMPLICATIONS, AND TREATMENT

Gilbert N. Casady, M.D., Daniel C. Moore, M.D.
and
L. Donald Bridenbaugh, M.D., Seattle

In a study of 8,000 deliveries performed under continuous caudal block analgesia, the records of 741 women indicated that the combined effect of a vasoconstrictor and an oxytocic drug, given three to six hours apart, led to severe hypertension in 34 (4.6% of 741) patients. These findings suggest that the patient's need for prophylactic administration of vasoconstrictor drugs in conjunction with caudal block analgesia in obstetrics should be evaluated before giving them. Treatment with chlorpromazine hydrochloride, to prevent the severe and disabling complications of postpartum hypertension, is essential.

Because of the many advantages for both the mother and the baby, the number of deliveries performed each year with use of subarachnoid (spinal) block, caudal block, epidural block, and pudendal block anesthesias is steadily increasing. When a subarachnoid, caudal, or epidural block is administered, vasoconstrictor drugs may be used intravenously or intramuscularly to prevent or correct a precipitous fall in blood pressure. If local infiltration of the perineum or pudendal block is used, the local anesthetic solution often contains a vasoconstrictor drug to prolong analgesia and prevent rapid absorption of the local anesthetic agent. During or immediately after the delivery of a baby, it is not unusual for an oxytocic drug to be given.

Too few physicians are aware that a severe, persistent, dangerous hypertension and even rupture of a cerebral blood vessel which may cause brain damage and hemiplegia can result from the combined effect of a vasoconstrictor and an oxytocic drug which have been administered to a patient within three to six hours of one another. Further study of this problem was prompted by the admission on Nov. 8, 1957, of a patient who had sustained a subarachnoid hemorrhage due to rupture f an intracranial aneurysm within two hours after ivery. The patient had received a caudal block; the caudal block was initiated, a vasocon- drug was administered prophylactically intramuscularly to prevent any fall in blood pressure. An oxytocic agent was administered at the time of placental delivery.

Method of Study

On Oct. 1, 1952, the department of anesthesiology at the Virginia Mason Hospital initiated a 24-hour record-keeping system of all obstetric anesthesias administered there that has continued to date. All anesthesias are administered by physician anesthetists, and these anesthesias and much of the obstetric data are recorded on a key sort-type record.[1] Most of the deliveries are performed with use of regional block procedures.

Department of Anesthesiology, the Mason Clinic and Hospital.
e Section on Obstetrics and Gynecology at the 108th
f the American Medical Association, Atlantic City,

subclavius muscle. The patient in case 1 (table 1) had a small, poorly formed clavicle which was thought to be related to inferior embryonic differentiation of the primary ossification centers. It should be emphasized, however, that by far the most important cause of nonunion in the middle third of the clavicle has been improper initial operation.

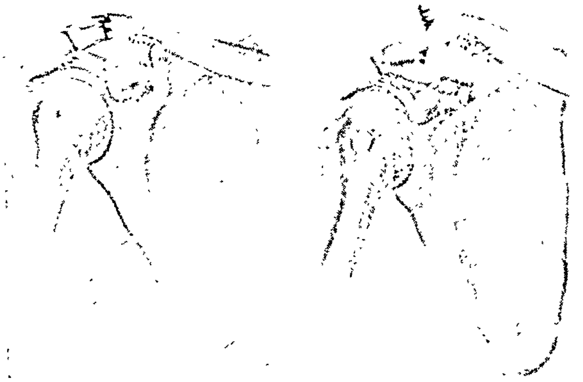

Fig. 1.—Fractures of outer third of clavicle with, *left*, coracoclavicular ligaments intact and, *right*, tear of coracoclavicular ligaments. Latter fracture is unstable and accounts for delayed union and nonunion in this portion of clavicle.

Pathological Findings.—Two distinct pathological types were seen. Type 1 was characterized by a false joint, with hyaline-like cartilage capping the dense bone ends, and possibly joint fluid. This was present in 10 patients. In the eight other patients the findings were quite different. These type 2 lesions consisted of resorption of the bone adjacent to the fractures, resulting in tapering bone ends, obliteration of the medullary canal, and a gap which was filled with fibrous tissue. These two distinct pathological types were best accounted for on the basis of infection or excessive bone removal in the second group. Surgical repair in patients with fractures of this type was more difficult because of the loss of bone substance. The gap was, at times, up to 3 cm. (fig. 2).

TABLE 2.—*Causal Factors in Eighteen Patients with Nonunion of Clavicle*

Site of Injury	Patients, No.
Outer one-third (4 patients)	
Tear of coracoclavicular ligament	4
Unconscious patient	1
Middle one-third (14 patients)	
Initial operation	10
Severe injury	10
Rotated fragment	2
Unconscious patient	1
Underdeveloped clavicle	1

In the case of outer third nonunions, the disrupted coracoclavicular ligaments became partially ossified (fig. 3).

Symptoms.—Weakness, pain, clicking, or deformity were usually great enough to cause th patient to desire repair of the defect. However seven patients were not sufficiently disabled to wis surgery. All female patients, with one exception sought correction; they were unwilling to accep the cosmetic defect, aside from other disabilitie Male patients were unconcerned with the appea ance but required relief of pain and fatigue. N instance of vascular or neurological impairment was encountered in this series.

Treatment

No difficulties were seen after repair of nonunio in patients with type 1 pathological findings. I these cases, good bone for securing end-to-end contact was present. Adequate length remained after freshening and opposing the bone ends, so that there was no tendency for distraction. Contact could be maintained easily. A minimum of 12 weeks is required for healing.

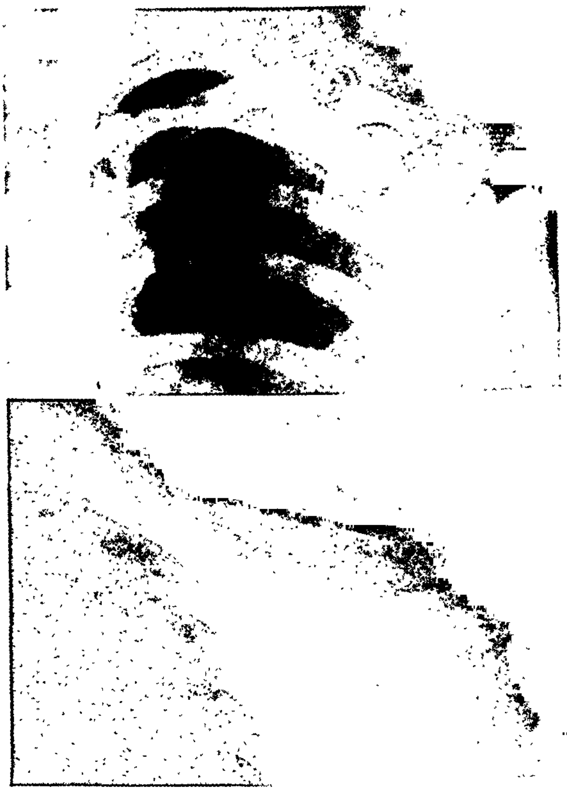

Fig. 2.—Pathological types of nonunion of clavicle: *top*, type 1, showing good bone length and false joint; *bottom*, type 2, showing resorption and tapering of bone ends. Note gap in second type.

Failure to regain bone union was limited to patients with nonunion of type 2. Repair was done in six of these and failed in three. In each failure (cases 12, 13, and 14), tibial or iliac grafts were used to span the gap, and contact of the ends of the clavicular fragments was not maintained. Furthermore, a greater risk of reactivation of infection was evidenced in the reconstruction of type 2 lesions. Nevertheless, when secure approximation of the ends of the clavicle was maintained by internal fixation for an adequate period, union occurred (cases 9 and 16). The resultant shortening did not produce brachial plexus or vascular pressure symptoms. In one instance, the subclavian vein was torn during the freeing of the bone ends, reminding us of the intimate relationship between this vessel and the scar tissue.

Fig. 3.—Ununited fracture of outer third of clavicle. Associated ossification of coracoclavicular ligaments depicts true extent of lesion.

It was consistently observed that wire loop suture alone could not control angulatory displacement of the clavicle. An intramedullary rod did not eliminate rotary movement and rarely prevented distraction. It was obvious that the patient could shrug the shoulder in a spica and that this form of fixation was also incomplete. In view of the difficulty of maintaining contact and alignment in those patients with lesions in which resorption was present (type 2), all three forms of fixation were required. However, patients with type 1 pseudarthroses could be treated adequately by simpler methods (fig. 4).

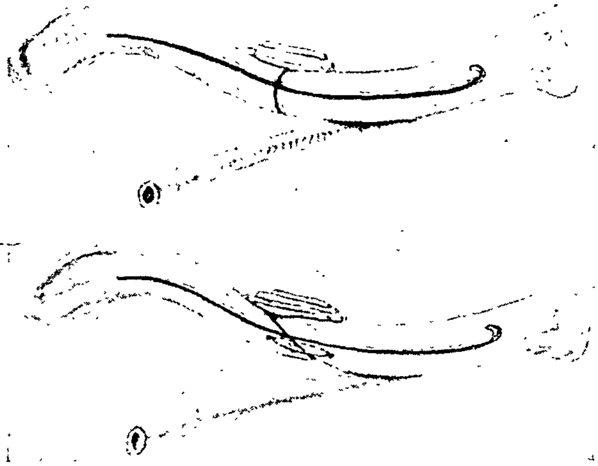
Fig. 4.—Repairs of middle third nonunion of clavicle. Ends of fragments are freshened. Intramedullary nails are inserted from medial to lateral away from subclavian vessels. Grafts are placed posteriorly. Type 2 lesions require wire loop suture to maintain contact and eliminate gap.

Patients with symptomatic outer third nonunions needed surgical repair rather than excision of the outer fragment, as has been recommended by some surgeons,[5] because the accompanying coracoclavicular ligament disruption allowed the stump of the proximal portion to be pulled upward, becoming prominent and requiring repeated excisions (fig. 5). Either the ununited fracture or the ligaments must be repaired, and the former is usually preferable (fig. 6).

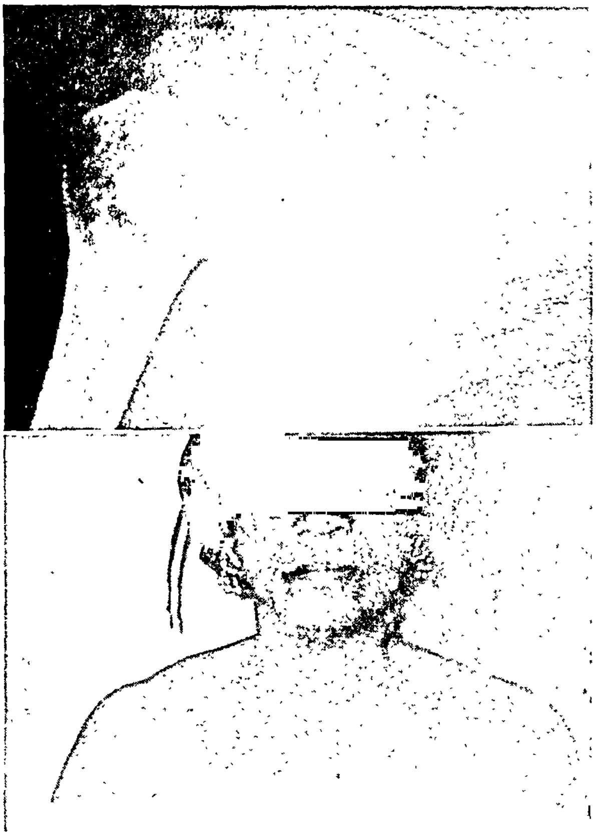
Fig. 5.—*Top,* error of excision of outer fragment for treatment of outer third nonunion. Disrupted ligaments allow clavicle to pull upwards. *Bottom,* patient's fracture required repeated excisions. If outer fragment must be excised, coracoclavicular ligaments should be reconstructed.

Excision of part or all of the clavicle was done in three patients with pathological fractures who are not included in this series. The results after these procedures indicated that loss of the clavicle weakened overhead hold and produced shoulder asymmetry. The result was inferior to that after repair. It was thought that this procedure should be used only for relief of brachial plexus or vascular symptoms or in selected patients with pathological fractures whose life expectancy is limited.

Nonunion of the Clavicle in Children.—Defects in children should be considered separately, because it is impossible to differentiate positively between congenital pseudarthrosis due to failure of development and traumatic defect. Three children under 12 years of age were seen who were thought to have ununited birth fractures. In each, the lesion was unilateral and had been noted for the first time when the child was 2 to 3 months of age, and the "tumor" increased in size as the child grew older. Roentgenography indicated middle third defects with ample bone substance and a false joint (fig. 7). There were no associated congenital anomalies elsewhere in the body. Repair was easily accomplished because there was adequate length. The embryologist[6] and radiologist[7] at our center believed that these lesions had the characteristics of ununited fractures rather than developmental defects. It therefore seems probable that they should be differentiated from neurofibromatosis or failure of development, especially because their prognosis after repair is so much better.

Comment

Open reduction and internal fixation constitute the preferred procedure in a few specific patients with clavicular fractures, e. g., those with fractures of the outer third associated with tears of the coracoclavicular ligaments, middle third fractures with rotation of a large intermediate fragment, soft tissue interposition, or vascular or brachial plexus compression. Operative treatment may also be necessary for immobilization in certain patients with multiple injuries or coma. It may even be justified electively, at times, on the basis of the convenience it might afford certain patients. However, the increased incidence of complications after elective surgery on the clavicle must be weighed in the decision, and, in any case, operative procedures must be done with greater care than they have been in the past.

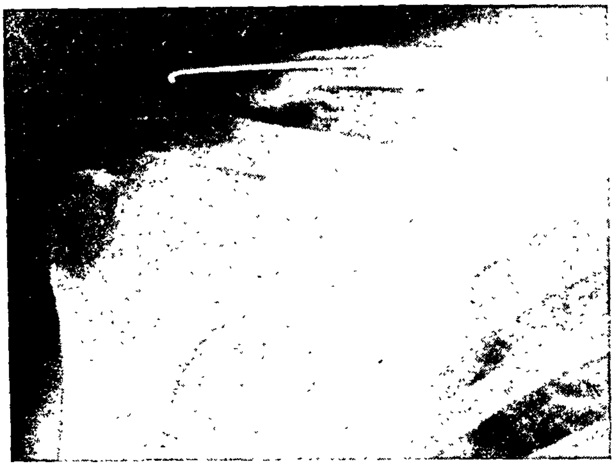

Fig. 6.—Repair of outer third nonunion. This is generally best accomplished by reestablishing bone union.

Summary and Conclusions

A series of 18 patients with ununited fractures of the clavicle is presented. Four fractures were in the outer third and 14 were in the middle third. The clavicle is not "invincible." Lack of immobilization, as in comatose patients, may result in nonunion. Delayed union or nonunion of fractures of the outer third is produced by the instability associated with tears of the coracoclavicular ligaments. Outer third fractures with concomitant ligamentous disruption are best treated by internal fixation, in distinction to fractures in which the ligaments are intact. By far the most frequent cause of nonunion of fractures in the middle third has been improper initial operation. Operation here must be done with the same regard for soft part attachments and fixation as in other open reductions.

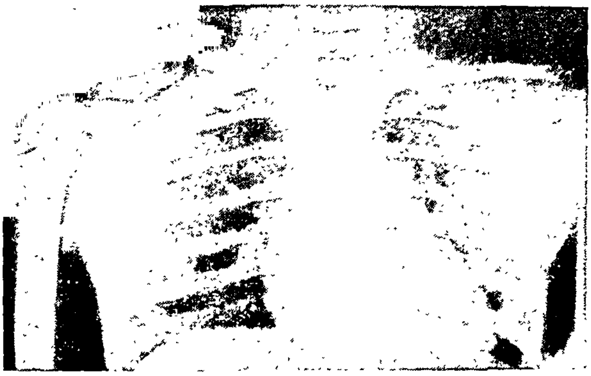

Fig. 7.—Probable nonunion of birth fracture. Although it is impossible to differentiate this from pseudarthrosis due to defective development, it seems probable that certain of these lesions, such as one shown, are actually ununited birth fractures.

Nonunion of the clavicle usually produces sufficient deformity and symptoms to require treatment. Treatment should consist of the reestablishment of bone continuity rather than excision, except when the lesion is producing pressure on the brachial plexus or subclavian vessels or in pathological fractures in patients whose life expectancy is limited. Bone union is more apt to occur if end-to-end contact of the fragments is maintained rather than the gaps bridged with bone grafts.

180 Fort Washington Ave. (32).

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POSTPARTUM HYPERTENSION AFTER USE OF VASOCONSTRICTOR AND OXYTOCIC DRUGS

ETIOLOGY, INCIDENCE, COMPLICATIONS, AND TREATMENT

Gilbert N. Casady, M.D., Daniel C. Moore, M.D.
and
L. Donald Bridenbaugh, M.D., Seattle

In a study of 8,000 deliveries performed under continuous caudal block analgesia, the records of 741 women indicated that the combined effect of a vasoconstrictor and an oxytocic drug, given three to six hours apart, led to severe hypertension in 34 (4.6% of 741) patients. These findings suggest that the patient's need for prophylactic administration of vasoconstrictor drugs in conjunction with caudal block analgesia in obstetrics should be evaluated before giving them. Treatment with chlorpromazine hydrochloride, to prevent the severe and disabling complications of postpartum hypertension, is essential.

Because of the many advantages for both the mother and the baby, the number of deliveries performed each year with use of subarachnoid (spinal) block, caudal block, epidural block, and pudendal block anesthesias is steadily increasing. When a subarachnoid, caudal, or epidural block is administered, vasoconstrictor drugs may be used intravenously or intramuscularly to prevent or correct a precipitous fall in blood pressure. If local infiltration of the perineum or pudendal block is used, the local anesthetic solution often contains a vasoconstrictor drug to prolong analgesia and prevent rapid absorption of the local anesthetic agent. During or immediately after the delivery of a baby, it is not unusual for an oxytocic drug to be given.

Too few physicians are aware that a severe, persistent, dangerous hypertension and even rupture of a cerebral blood vessel which may cause brain damage and hemiplegia can result from the combined effect of a vasoconstrictor and an oxytocic drug which have been administered to a patient within three to six hours of one another. Further study of this problem was prompted by the admission on Nov. 8, 1957, of a patient who had sustained a subarachnoid hemorrhage due to rupture of an intracranial aneurysm within two hours after delivery. The patient had received a caudal block; when the caudal block was initiated, a vasoconstrictor drug was administered prophylactically intramuscularly to prevent any fall in blood pressure. An oxytocic agent was administered at the time of placental delivery.

Method of Study

On Oct. 1, 1952, the department of anesthesiology at the Virginia Mason Hospital initiated a 24-hour record-keeping system of all obstetric anesthesias administered there that has continued to date. All anesthesias are administered by physician anesthetists, and these anesthesias and much of the obstetric data are recorded on a key sort-type record.[1] Most of the deliveries are performed with use of regional block procedures.

From the Department of Anesthesiology, the Mason Clinic and Virginia Mason Hospital.

Read before the Section on Obstetrics and Gynecology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

When the patient mentioned above was admitted on Nov. 8, 1957, it was decided to review the 10,383 obstetric anesthesias which had been administered since 1952, and, as from November, 1957, all cases were to be studied carefully. Particular care was taken to record the medicaments administered, blood pressure, pulse rate, and other data on the hospital chart and the key sort record of each patient.

A screening of the obstetric anesthesia records from October, 1952, to November, 1957, revealed that of 10,383 anesthesias administered in deliveries, about 62% (6,400) had been continuous caudal analgesias. The rest of the mothers had received epidural block, spinal block, or general anesthesia. During this period, the percentage of deliveries in which continuous caudal block was administered had risen from 29% in 1952 to 82% in 1957.[1] Of a total of 2,135 obstetric anesthesias administered in 1958, 1,750 (82%) were continuous caudal blocks.[1] Inasmuch as continuous caudal analgesia was used in the majority of cases, and since at least 98% of these patients had, at initiation of the caudal block, received a vasoconstrictor drug to prevent hypotension as well as an oxytocic drug at the time of placental delivery, it was decided to include in this study only mothers who had received continuous caudal block anesthesias.

Analysis of Thirty-four Cases of Postpartum Hypertension in Relationship to Drugs Administered During Labor, November, 1957, to April, 1958

Drugs	No. of Patients
Vasoconstrictor and oxytocic	
Methoxamine and ergonovine maleate	21
Methoxamine and methylergonovine	6
Methoxamine and oxytocin	1
Methoxamine and oxytocin and methylergonovine	1
Total	29
Oxytocic (only)	
Ergonovine maleate	2
Methylergonovine	1
Oxytocin	1
Total	4
None	1
Total	34

Results

From October, 1952, to May, 1955, about 2,200 patients who received continuous caudal block analgesia were given a prophylactic dose of 25 to 50 mg. of ephedrine sulfate. From May, 1955, to November, 1957, about 4,200 patients who were delivered under continuous caudal block received a prophylactic intramuscular dose of 8 to 12 mg. of methoxamine (Vasoxyl) hydrochloride. The latter drug was substituted for the ephedrine sulfate primarily because of its longer duration of action. At the time of delivery of the placenta, most of these 6,400 patients received ergonovine (Ergotrate) maleate, 1/320 grain (0.23 mg.), or methylergonovine (Methergine) maleate, 0.2 mg., while a few received oxytocin (Pitocin), 10 units. Unfortunately, the incidence of postpartum hypertension in these 6,400 patients is unknown. Although some patients complained of headache, the seriousness and significance of this symptom was not recognized, because no grave sequelae developed. Therefore, only symptomatic treatment was instituted, and accurate data concerning the headache (i. e., its duration and whether or not it was associated with hypertension) were not recorded.

From November, 1957, to April, 1958, 741 patients received caudal block analgesia, and each drug used and its relationship to subsequent symptoms was carefully recorded. The records revealed that 737 (99.5%) of these patients received a prophylactic dose (8 to 12 mg.) of methoxamine hydrochloride at initiation of the caudal block and an oxytocic drug, primarily ergonovine maleate (1/320 grain) or methylergonovine maleate (0.2 mg.), at *the time of placental delivery. Thirty-four* (4.6) of the 741 patients developed postpartum hypertension, with systolic blood pressures of 140 mm. Hg or higher. Fourteen of these patients developed diastolic blood pressures of about 90 mm. Hg, and 20 developed diastolic pressures of 100 mm. Hg or higher. The last one in this series of patients who developed postpartum hypertension from administration of this combination of drugs ruptured an aneurysm. This event terminated the routine prophylactic administration of a vasoconstrictor drug.

Analysis of the drugs given to the 34 hypertensive patients showed that (1) 29 had received methoxamine (8-12 mg.) prophylactically and an oxytocic drug (ergonovine maleate, 1/320 grain [0.23 mg.]; or methylergonovine maleate, 0.2 mg., or oxytocin, 10 units, or both); (2) 4 patients had not been given a vasoconstrictor drug, because toxemia was suspected, but had received an oxytocic drug; and (3) one patient had received neither a vasoconstrictor nor an oxytocic drug (see table). The dose of the methoxamine hydrochloride did not seem to be of significance, 15 patients having received 10 mg. of the drug, 9 patients 12 mg., and 5 patients 8 mg. The average interval from administration of the vasoconstrictor drugs to the onset of hypertension was one hour and 51 minutes, with a range from 50 minutes to six hours and 50 minutes. The average interval from administration of the oxytocic drugs to the onset of hypertension was 39½ minutes, with a range from 10 to 80 minutes.

Headache, the *most common symptom* of these patients, occurred in about 80% of cases. It was severe, incapacitating, difficult to relieve, and involved the frontal, parietal, and occipital areas of the head. Some of the patients were irritable; a few seemed disoriented.

The 741st patient during this phase of the study sustained a *subarachnoid hemorrhage*. This 28-year-old multiparous patient was admitted at full term, in normal labor. Her obstetric anesthesia record and her prenatal chart showed nothing unusual. She had received methoxamine hydrochloride, 10 mg. intramuscularly, at 12:15 a. m., at initiation of the continuous caudal anesthesia. Three subsequent injections of the anesthetic drug, at about 45-minute intervals, were administered uneventfully, and she had a normal delivery. After delivery of the placenta at 2:40 a. m., ergonovine maleate, 1/320 grain, was given intramuscularly. She was normotensive (blood pressure of 120/76 mm. Hg) prior to, during, and at completion of the delivery.

Inspection of the nurses' notes revealed that shortly after the patient was returned to her room, at 3:00 a. m., her blood pressure rose to 150/70 mm. Hg. At 3:15 a. m. the hypertension became severe, with a blood pressure of 180/120 mm. Hg, at which time she complained of severe headache. This was known to the nurse in charge, who notified the obstetrician; he, in turn, ordered intramuscular administration of 75 mg. of meperidine (Demerol) hydrochloride. Apparently during the next five minutes the aneurysm ruptured, because by 3:20 a. m. she had difficulty in speaking. The department of anesthesiology was notified at 4:15 a. m., at which time her blood pressure was 162/100 mm. Hg. She was then given chlorpromazine hydrochloride, 12.5 mg., intravenously. Her blood pressure returned to within normal limits (130/60 mm. Hg) almost immediately.

About eight hours later a neurological examination was performed: motor aphasia, right-sided facial weakness, weakness in the arms, and a positive Babinski sign on the right side were present. The spinal fluid was grossly bloody. Recovery of this patient has been slow. At the time of writing she has motor aphasia and is receiving speech training.

Comment

While hypertension and even subarachnoid hemorrhage are known to occur during any stage of pregnancy, regardless of the quality of the obstetric care given or the anesthetic technique used, they are more apt to develop during the last trimester and in the postpartum period.[2] This discussion is limited primarily to the hazards of the hypertension which may develop in the postpartum period when administration of a regional block anesthetic is accompanied by combined use of a vasoconstrictor and an oxytocic drug.

Etiology of Postpartum Hypertension.—Known physiological and pharmacological mechanisms may produce sudden postpartum hypertension from either relative or actual overloading of the total vascular compartment. The known physiological causes are the hypervolemia normally present during pregnancy and the sudden shift of blood from the uterine vascular space after delivery. The known pharmacological causes are (1) constriction of the blood vessels due to administration of a vasoconstrictor drug, given to prevent or correct a fall in blood pressure which results from administration of a regional block procedure, (2) contraction of the uterus which is effected by use of an oxytocic drug, and (3) vasoconstrictor effect of an oxytocic drug on the blood vessels. It must be stressed that the synergistic and additive vasoconstrictive effects of a vasoconstrictor and an oxytocic drug, when both are given, may be far out of proportion to the expected reaction to separate administration of either of these drugs.[3]

In addition to the above known possible causes of overloading of the cardiovascular system, other as yet unknown intrinsic factors may be involved in some of these cases, for a few patients received neither a vasoconstrictor nor an oxytocic drug.

Treatment of Postpartum Hypertension.—It was obvious almost from the beginning of the phase of the study which started in November, 1957, that the problem of postpartum hypertension resulting from the combined use of a vasoconstrictor and an oxytocic drug had to be treated not only symptomatically but definitively. The patients' headaches were intolerable and the hypertension dangerous. Neither the severe, persistent headache nor the hypertension was relieved by therapy with codeine, magnesium sulfate, meperidine hydrochloride, morphine, alkaloids of opium (Pantopon), phenobarbital (Luminal) sodium, or promethazine (Phenergan) hydrochloride either alone or in various combinations.

Because of the adrenolytic action of chlorpromazine (Thorazine) hydrochloride, it was decided to find out whether it would resolve the severe hypertension resulting from the combined use of a vasoconstrictor and an oxytocic drug. The intravenous route was selected, because these patients must be treated immediately if serious sequelae, e. g., hemiplegia, are to be avoided. Chlorpromazine hydrochloride (25 mg.) was given intravenously for the first time to a former nurse employee of the hospital who had developed postpartum hypertension with a blood pressure of 180/130 mm. Hg, a severe headache, and signs of mild disorientation. Methoxamine hydrochloride (12 mg.) had been given at initiation of the caudal anesthesia three hours prior to delivery, and ergonovine maleate (1/320 grain) had been given at the time of placental delivery. After administration of the chlorpromazine hydrochloride, the patient's blood pressure promptly returned to a normal of 120/70 mm. Hg and remained normal, but she became unresponsive for several hours, presumably because of the effect of the chlorpromazine. Her failure to respond was attributed to that drug, because she showed no evidence of a complication, such as cerebral accident, resulting from the hypertension, when she had recovered from the effects of the chlorpromazine eight hours later. Therefore, the dose given to other patients has ranged from 12.5 to 15 mg. This is given immediately intravenously, at a rate of 2.5 mg. every 15 seconds, until there is either a satisfactory reduction in blood pressure or 12.5 to 15 mg. of the drug has been given.

To calibrate the administration of the chlorpromazine hydrochloride, 1 cc. (25 mg.) of the drug is diluted to 10 cc. in a 10-cc. syringe by the addition of 9 cc. of isotonic sodium chloride solution or distilled water. Then each cubic centimeter of solution contains 2.5 mg. of chlorpromazine hydrochloride and may easily be injected as stated. If, after injection of 15 mg. of chlorpromazine hydrochloride, the patient's blood pressure has not fallen to normal, at least two minutes should be allowed to pass before more of the drug is given. Intravenous administration of chlorpromazine hydrochloride must be carefully done, especially if the effects of a subarachnoid block, an epidural block, or a caudal block are still present. Too large a dose of chlorpromazine or too rapid administration, or both, in the presence of one of these types of analgesia, may result in a precipitous fall in blood pressure.[3]

The indications for treatment with chlorpromazine hydrochloride are sustained elevation of the systolic blood pressure above normal, e. g., an increase of 30 to 40 mm. Hg or a sustained diastolic pressure of 90 mm. Hg or more, or both, with or without a severe, persistent headache. It is believed that the rise in diastolic pressure is the most significant component in the elevations of blood pressure and that the sustained elevation of the diastolic pressure is responsible for severe headache and rupture of a cerebral blood vessel. The onset of the effect of chlorpromazine hydrochloride has been rapid, usually occurring in less than two minutes. Ten patients in all have received chlorpromazine hydrochloride. In nine patients the blood pressure has returned to normal and remained so, but one patient, in whom the drug was effective but whose blood pressure rose again with subsequent oral administration of ergonovine maleate, 1/320 grain, required another injection of 12.5 mg. of chlorpromazine hydrochloride.

Need for Prophylactically Given Vasoconstrictor Drugs.—It was once believed that, since vasoconstrictor drugs did no particular harm in the patient who showed no evidence of disorders such as eclampsia, they could be given prophylactically to insure that the systolic blood pressure would not fall below 80 mm. Hg during labor; this, of course, was done to prevent fetal anoxemia.[4] Because of the severe sequelae from the combined use of a vasoconstrictor and oxytocic drug, the real need for prophylactic administration of a vasoconstrictor drug was determined in each of our patients.

From April, 1958, to October, 1958, the routine prophylactic use of vasoconstrictor drugs was discontinued and 727 caudal blocks were administered. Hypotension was treated when it occurred. Sixty-four (8.8%) of these patients developed hypotension with a systolic blood pressure of 80 mm. Hg or less. The fall in blood pressure was easily corrected. Sixty-two patients received ephedrine sulfate, 15 mg. intravenously and 35 mg. intramuscularly. Two received methoxamine hydrochloride, 12 mg. intramuscularly. There were no instances of fetal distress in babies delivered from these mothers. Ephedrine sulfate was selected as the preferred vasoconstrictor drug in most of these patients, since its duration of action is shorter than that of methoxamine hydrochloride.

During this period there were 15 (2%) instances of hypertension. Three patients had received ephedrine sulfate to correct hypotension due to caudal anesthesia induced one hour prior to their delivery but were not given an oxytocic drug at the time of delivery. Nine patients had received oxytocic drugs only (five were given ergonovine maleate, 1/320 grain, and four methylergonovine maleate, 0.2 mg.). Three patients had received neither drug. None of these 15 patients had severe hypertension and none met the requirements for treatment with chlorpromazine hydrochloride; had any of them met the requirements stated previously, the drug would have been administered.

Summary and Conclusions

Nine patients who had postpartum hypertension with rupture of a cerebral vessel after injection of a vasoconstrictor drug, or an oxytocic drug, or both, have been cited in the literature.[5] Nonetheless, from our experience and discussion of this problem with other physicians, it seems reasonable to conclude that most physicians are not aware of the dangers of administration of a vasoconstrictor in conjunction with an oxytocic drug. The factors that must be stressed are as follows: 1. If possible, postpartum hypertension due to the combined effect of a vasoconstrictor and an oxytocic drug must be prevented. The clinical severity of the symptoms of hypertension makes this desirable; the possibility of a subarachnoid hemorrhage makes it mandatory. 2. Prophylactic administration of vasoconstrictor drugs should be omitted when regional block anesthesia is used in vaginal delivery. When this was done, the incidence of hypertension dropped from 4.6 to 2%. Hypotension was not a problem in these patients. In a case in which a vasoconstrictor drug was used to correct hypotension due to the administration of caudal block anesthesia, the obstetrician was notified and he refrained from giving an oxytocic drug. While oxytocin has been recommended in preference to ergonovine or methylergonovine maleate when use of a vasoconstrictor drug is necessary, this study indicates that it, too, can be dangerous. 3. The physician anesthetist, the obstetrician, and, in particular, the nurses must be made aware of this problem and its significance. The nurse must immediately notify either the obstetrician or the physician anesthetist when hypertension or headache occurs in a patient. When sudden, marked elevation of blood pressure, particularly of the diastolic component, occurs, prompt treatment with chlorpromazine hydrochloride is mandatory. 4. While this paper deals primarily with administration of continuous caudal block anesthesia and vaginal delivery, the hazards of the concomitant use of a vasoconstrictor and an oxytocic drug exist regardless of the type of anesthesia induced or whether or not it is given to pregnant women or other patients.

Postpartum hypertension, frequently unrecognized in the form of a severe headache, is a general hazard accompanying delivery which can result in cerebrovascular injury. In a study of about 8,000 deliveries that had been performed under continuous caudal block analgesia, the complete and detailed records of 741 patients pointed to the conclusion that the combined effect of a vasoconstrictor and an oxytocic drug, given three to six hours apart at initiation of the caudal block and at the time of placental delivery, respectively, led to severe hypertension in 34 (4.6%) of 741 patients, one of whom also suffered cerebrovascular injury. Treatment with chlorpromazine hydrochloride, to prevent the severe and disabling complications of postpartum hypertension, is essential. These findings suggest that the need for prophylactic administration of vasoconstrictor drugs in conjunction with caudal block analgesia in obstetrics is doubtful.

1118 Ninth Ave. (1) (Dr. Moore).

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RELATION OF DRUG RESISTANCE TO ENZYME ACTIVITY AMONG COLIFORM BACTERIA

NEW APPROACH TO PROBLEM

Harry Seneca, M.D., Hans H. Zinsser, M.D.
and
John K. Lattimer, M.D., New York

Aerobacter aerogenes, which readily undergoes mutations that increase its resistance to antibiotics, is also able to exist on certain substrates on which Escherichia coli cannot exist. Since Esch. coli mutates less readily and has less capacity for developing forms resistant to antibiotics, the question arises whether this relationship between mutability and substrate-preferences is generally valid. Fifty-one varieties of bacteria were grouped according to their ability to decompose urea and citrate in culture mediums and then tested for susceptibility to six antibacterial agents. Although some discrepancies were found, the suggested principle generally held true. Therefore the finding of citrase and urease activity in an organism is of practical significance. The fact that these enzyme systems are so important to some organisms suggests a new avenue of attack on drug-resistant infections.

Among bacteria commonly found in urologic patients there has been rapid development of resistance to all antibiotics available for clinical therapy.[1] This has led us to analyze, in greater detail, the type of metabolism manifested in particular by Aerobacter, Proteus, and Pseudomonas organisms. It has seemed logical to correlate the escape of these organisms from antibiotic control with their adaptation to survival on the relatively simple substrates to be found in high concentration in urine. Notable among the substrates of value for bacterial nutrition are urea, ammonium ion, and citrate ion. We have made a detailed analysis of the enzymatic capacities of organisms, provided from patients at the Squier Urological Clinic, to utilize ammonia, urea, and citrate. More subtle facets of vitiation of some antibiotics by the high salt concentrations present in the urine, such as the phosphate antagonism to the tetracyclines, have not been studied in detail but will form the basis for additional studies.

From the Department of Urology, Columbia University College of Physicians and Surgeons, and Presbyterian Hospital.

The capacity to mutate rapidly, shown by us in strains of Aerobacter aerogenes, may be linked to the simple substrates on which A. aerogenes can exist, but this is not easily susceptible of proof from the data available to us. Clinically it is apparent, however, that Escherichia coli, which is unable to mutate with ease and probably has a lower rate of mutation, is unable to exist on the simple substrates which A. aerogenes can tolerate. Bacterial mutation induced by changes in the available substrates has been evidenced by the antagonisms of these by other naturally occurring substrates.[2] There is excellent correlation between the capacity to utilize both citrate and urea and the capacity to develop resistant forms.

Methods

Antibacterial spectrums were determined with use of the tube dilution method for establishing the minimum inhibitory concentrations (MIC) of several antibiotics (tetracycline, chloramphenicol, erythromycin, and a combination of equal amounts of penicillin and streptomycin) and two antibacterial chemicals (sulfadiazine and nitrofurantoin). These drugs were serially diluted in sterile Kahn tubes containing 0.5 ml. of brain-heart infusion broth. To each tube was then added 0.5 ml. of inoculum of overnight culture diluted 10^{-3} in brain-heart infusion broth, in the case of the antibiotics and nitrofurantoin, and 10^{-10} for sulfadiazine. Final concentrations for sulfadiazine ranged from 5 to 0.19 mg., and for the other drugs from 100 to 0.19 mcg., per milliliter. These tubes were incubated overnight and readings for drug susceptibility were taken.

An enzyme profile, which made use of their ability to split urea and utilize citrate either in combination or singly, was determined for each of the varieties of bacteria tested. Variations in the amount of urease activity were also taken into account.

In the test for ability to split urea, a urea agar medium was employed and the test for citrase activity on the medium was done on a citrate agar medium.[3] Slants of urea agar and citrate agar were streaked from broth cultures and readings were taken after 24, 48, 72, and 96 hours of incubation at 37 C. The following categories were differentiated: no growth, growth, change of color of slant, and change of color of both slant and butt of the culture tube. If urea was split by the organism, the phenol red indicator caused the medium to become red. When there was excessive urease activity manifested, the entire medium became red; but if the urease activity was on a limited scale, only the slant became red. In the citrate medium, the indicator was bromothymol blue. When the citrate in the medium was utilized, it indicated the presence of citrase activity, which caused the medium to become blue (the original color of the medium was green). Some bacteria showed no evidence of citrase or urease activity on these mediums.

Results

In table 1 the bacteria tested are provisionally classified on the basis of ability to split urea or utilize citrate, or both. The group-1 organisms both split urea and utilized citrate, and their urease activity was the greatest of any of the strains tested, as manifested by the fact that not only the slant but also the butt of the tube underwent a color change because of the indicator in the medium, even under reduced aerobic conditions. In this group were the strains of highly resistant B. proteus organisms recovered from the urinary tracts of patients at the Columbia-Presbyterian Medical Center and designated in the table as B. proteus columbiensis, with several strains designated by the names Reilly or Dobriner or such numbers as 271 and 198, plus the letters CP (Columbia-Presbyterian). According to Bergey, these organisms are Proteus vulgaris, Proteus rettgeri, and Proteus mirabilis. All of these strains were highly resistant to most of the drugs tested. A strain of B. proteus OX2, obtained from the U. S. Army, also fell into this group, although, as far as is known, this strain has never been exposed clinically to any antibiotics.

Group 2 was made up of organisms which split urea; in which the urease activity was of only moderate intensity, causing a color change in only the slant of the culture; but which also utilized citrate. Aerobacter aerogenes was the member of this group which showed the maximum drug resistance. Klebsiella pneumoniae also showed both urea-splitting activity (mild) and citrate-utilizing ability but was only moderately resistant to the drugs tested. We cannot yet say whether this organism represents an exception which runs contrary to the proposed thesis that capacity for drug resistance and these enzyme activities exist together or whether this organism has an unsuspected capacity for developing resistance to high levels of drugs. Some strains of Pseudomonas aeruginosa have urease and citrate activity.

Organisms in both groups 3 and 4 split urea but failed to utilize citrate. Those in group 3 differed from group 4 in that they showed less intense urease activity. In group 3 was B. proteus morganii and in group 4, B. proteus OX 19.

Organisms in group 5 did not split urea but did utilize citrate. The most resistant members of this group tested were strains of Pseudomonas aeruginosa, which definitely represented an exception to the thesis and were highly resistant to the drugs used but seemed highly sensitive to colistine methanesulfonate. Also in group 5 were Vibrio cholerae, strains of Inaba and Ogawa and a nonagglutinable vibrion, organisms of the genus Salmonella, and Alcaligenes fecalis. These organisms also utilized citrate and did not split urea but were relatively more sensitive to sulfadiazine, tetracycline, and chloramphenicol.

In group 6 were organisms which neither split urea nor utilized citrate. This group contained Escherichia coli, Eberthella typhosa, Shigella dysenteriae, Vibrio cholerae El Tor, and B. proteus OXK. This group as a whole showed high susceptibility to tetracycline and chloramphenicol and variable susceptibility to sulfadiazine.

TABLE 1.—*Enzyme Profile and Drug Resistance*[*]

		Enzyme Activity on Mediums		Drug Susceptibility					
Group	Organism and Source	Urease	Citrase	Nitrofurantoin	Sulfadiazine	Tetracycline	Chloramphenicol	Erythromycin	Penicillin and Streptomycin
1............	Bacillus proteus columbiensis	++++	+						
	Reilly (C P)[†]			100.0	5.00	100.0	100.0	100.0	12.5+12.5
	271 (C P)			100.0	5.00	100.0	100.0	100.0	12.5+12.5
	189 (C P)			100.0	5.00	100.0	50.0	100.0	25.0+25.0
	70 (C P)			100.0	5.00	100.0	100.0	100.0	50.0+50.0
	76 (C P)			100.0	5.00	100.0	6.25	100.0	3.1+3.1
	Dobriner (C P)			100.0	0.625	100.0	50.0	100.0	3.1+3.1
	B. proteus OX2 (U. S. Army)			25.0	0.19	0.78	0.19	100.0	0.78+0.78
2............	Aerobacter aerogenes	++	+						
	Pinkerton (C P)			100.0	5.0	100.0	25.0	100.0	50.0+50.0
	Arnone (C P)			100.0	5.0	100.0	50.0	100.0	50.0+50.0
	Leiboff (C P)			100.0	5.0	100.0	6.25	100.0	50.0+50.0
	Hegi (C P)			100.0	5.0	100.0	25.0	100.0	50.0+50.0
	Kostek (C P)			100.0	5.0	100.0	50.0	100.0	50.0+50.0
	Klebsiella pneumoniae	++	+						
	10031 FDA			6.25	0.156	0.19	0.19	3.125	0.39+0.39
	Type 1 U. S. Army			6.25	0.019	1.56	0.78	25.0	0.19+0.19
	Type 2 U. S. Army			6.25	0.3125	0.39	0.78	1.56	0.19+0.19
	Type 3 U. S. Army			50.0	0.78	3.125	3.125	25.0	0.78+0.78
3............	B. proteus morganii	++	—						
	407 U. S. Navy			100.0	0.019	12.5	100.0	100.0	12.5+12.5
4............	B. proteus OX 19	++++	—	50.0	0.009	3.12	0.19	6.25	0.78+0.78
5............	Pseudomonas aeruginosa	—	+						
	Bennefield (C P)			100.0	5.0	6.25	100.0	100.0	50.0+50.0
	Lampros (C P)			100.0	5.0	12.5	100.0	100.0	50.0+50.0
	324 (C P)			100.0	5.0	100.0	100.0	100.0	50.0+50.0
	594 (C P)			100.0	5.0	25.0	100.0	100.0	50.0+50.0
	Jones 23 (C P)			100.0	5.0	50.0	100.0	100.0	50.0+50.0
	Vibrio cholerae	—	+						
	Inaba 163 U. S. Army			6.25	0.31	0.19	0.39	0.78	6.25+6.25
	161 U. S. Army			3.125	0.078	0.19	0.39	0.78	6.25+6.25
	164 U. S. Army			3.125	0.078	0.19	0.39	0.39	6.25+6.25
	Ogawa 239 U. S. Army			12.50	0.625	50.0	0.78	0.78	3.12+3.12
	220 U. S. Army			6.25	0.156	0.19	0.19	0.78	3.12+3.12
	Nonagglutinable 188 U. S. Army			6.25	0.019	0.19	0.19	0.39	12.5+12.5
	Salmonella paratyphi Pfizer			6.25	0.078	0.19	0.19	25.0	6.25+6.25
	paratyphi ETS1 U. S. Army			25.0	0.312	0.78	0.78	50.0	6.25+6.25
	schottmülleri Pfizer			25.0	2.5	1.56	0.78	50.0	3.12+3.12
	schottmülleri ETS 3 U. S. Army			25.0	1.25	0.19	1.56	50.0	6.25+6.25
	paratyphi C U. S. Navy			25.0	0.312	0.19	0.39	12.5	0.39+0.39
	Alcaligenes fecalis U. S. Navy			100.0	0.009	1.56	50.0	100.0	3.12+3.12
6............	Escherichia coli Pfizer	—	—	12.5	5.0	0.39	1.56	25.0	6.25+6.25
	017 U. S. Army			25.0	0.62	1.56	1.56	50.0	12.5+12.5
	055 U. S. Army			50.0	5.0	1.56	1.56	50.0	6.25+6.25
	0126 U. S. Army			12.5	5.0	0.78	0.78	100.0	25.0+25.0
	Turkey strain U. S. Navy			25.0	5.0	0.78	6.25	50.0	6.25+6.25
	Eberthella typhosa H901 U. S. Army			12.5	0.62	0.39	0.39	25.0	6.25+6.25
	typhosa C P			25.0	0.078	0.78	1.56	50.0	3.12+3.12
	typhosa Pfizer			50.0	5.0	0.39	0.39	50.0	6.25+6.25
	typhosa Vi U. S. Navy			25.0	0.62	0.78	0.78	50.0	0.78+0.78
	Shigella dysenteriae 1 U. S. Navy			6.25	0.019	0.19	0.39	12.5	3.12+3.12
	dysenteriae 3			6.25	0.009	0.39	0.39	12.5	3.12+3.12
	flexneri 3			6.25	2.5	0.19	0.39	50.0	3.12+3.12
	boydii 2			6.25	0.31	0.39	0.78	50.0	6.25+6.25
	sonnei 2			6.25	1.25	0.19	1.56	50.0	6.25+6.25
	V. cholerae El Tor U. S. Army			25.0	5.0	0.19	1.56	50.0	3.12+3.12
	B. proteus OXK U. S. Army			50.00	0.019	100.0	1.56	100.0	0.19+0.19

[*] Minimum inhibitory concentration for sulfadiazine is in milligrams per milliliter; all others are in micrograms per milliliter.
[†] CP = Columbia-Presbyterian.

Comment

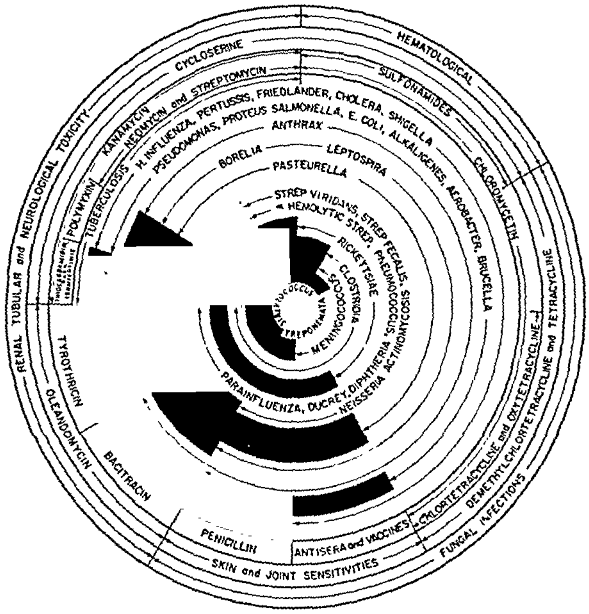
When each new antibiotic has been introduced, we have classified it on the basis of its antibacterial spectrum (see figure). With increasing usage of any one drug the spectrum of each drug has been reduced.[4] The fact that an orderly arrangement of organisms and drugs can be made suggests a fundamentally shared capacity in the organisms susceptible to the particular drug and in the host receiving them.

It is recognized that many more strains of these various families of organisms must be surveyed in order to test the suggested hypothesis that the capacity for drug resistance and urease and citrase activity usually exist together. Thus far, with the exception of Klebsiella and certainly Pseudomonas, it appeared that the bacteria which were active splitters of urea and utilizers of citrate either were drug-resistant or mutated easily to drug-resistant forms. Those organisms which only split urea (such as B. proteus morganii and OX 19) showed less tendency to mutate to highly drug-resistant forms than those which both split urea and utilized citrate. The same was true of the organisms which only utilized citrate, but these organisms in general tended to be more drug-susceptible than those which split urea as well. Those organisms which neither split urea nor utilized citrate tended to be much more drug-susceptible, and in other experiments thus far in this laboratory it has not been possible to produce mutants which were resistant to high levels of drugs, among the organisms in this group. The susceptibilities are shown in table 2.

Further discrepancies exist in groups 2 and 5, in that some strains in group 2, e. g., Klebsiella pneumoniae, which utilized citrate and split urea are drug-susceptible, while in group 5, in which only citrate is utilized but urea is not split, Ps. aeruginosa is drug-resistant, while V. cholerae, Salmonella, and A. fecalis are drug-susceptible.

Summary

Urologic infections with drug-resistant strains of Bacillus proteus, Aerobacter aerogenes, and Pseudomonas aeruginosa constitute a serious clinical problem. These families of bacteria have been demonstrated to mutate more rapidly to highly drug-resistant forms than such organisms as Escherichia coli. These particular bacteria also show enzymatic activity not demonstrated by Esch. coli. This is manifested, for example, by the splitting of urea (by urease) by some of these bacteria and by the capacity to utilize citrate as the sole source of carbon (via citrase) by still other bacteria of this group. The mechanism which permits these enzymes to act on substrates in their environment may be related not only to the presence of these enzymes within some of the bacteria, but also to differences in permeability of the bacterial cell membrane which permit these enzymes to act on the substrate.


HEMATOLOGICAL
SULFONAMIDES
CHLOROMYCETIN
TETRACYCLINE
DEMETHYLCHLORTETRACYCLINE and TETRACYCLINE
CHLORTETRACYCLINE and OXYTETRACYCLINE
FUNGAL INFECTIONS
ANTISERA and VACCINES
SKIN and JOINT SENSITIVITIES
PENICILLIN
BACITRACIN
OLEANDOMYCIN
TYROTHRICIN
RENAL TUBULAR and NEUROLOGICAL TOXICITY
POLYMYXIN
KANAMYCIN
NEOMYCIN and STREPTOMYCIN
CYCLOSERINE
TUBERCULOSIS
H. INFLUENZA, PERTUSSIS, FRIEDLANDER, CHOLERA, SHIGELLA
PSEUDOMONAS, PROTEUS SALMONELLA, E. COLI, ALKALIGENES, AEROBACTER, BRUCELLA
ANTHRAX
BORELIA
LEPTOSPIRA
PASTEURELLA
STREP VIRIDANS, STREP FECALIS,
HEMOLYTIC STREP, PNEUMOCOCCUS,
RICKETTSIAE
CLOSTRIDIA
STAPHYLOCOCCUS
TREPONEMATA
MENINGOCOCCUS
GONOCOCCUS
ACTINOMYCOSIS
PARAINFLUENZA, DUCREY, DIPHTHERIA
NEISSERIA

Common pathogens, arranged in sequence radially, and antibacterial compounds, on periphery, with ineffective sectors in black. Outside antibacterials are human toxic side-effects. It is likely that colistine methanesulfonate will overlap both polymyxin and kanamycin.

Table 2.—*Pathogenic Gram-Negative Bacilli*

Group	Enzyme Activity	
	Split Urea	Utilized Citrate
1.		
Bacillus proteus columbiensis	++++	+
B. proteus OX2	++++	+
2.		
Aerobacter aerogenes	++	+
Klebsiella pneumoniae	++	+
Pseudomonas aeruginosa	++	+
3.		
B. proteus morganii	++	−
4.		
B. proteus OX19	++++	−
5.		
Pseudomonas aeruginosa	−	+
Vibrio cholerae	−	+
Salmonella	−	+
Alcaligenes faecalis	−	+
6.		
Escherichia coli	−	−
Eberthella typhosa	−	−
Shigella dysenteriae	−	−
V. cholerae El Tor	−	−
B. proteus OXK	−	−

The presence of citrase activity has long been used as a means of identifying Ps. aeruginosa, and it now appears possible that quantitative and qualitative aerobic and anaerobic differences in urea-splitting ability may be a means for identifying and further subdividing the varieties of B. proteus, A. aerogenes, and Ps. aeruginosa.

Urease and citrase activity may be related to the capacity of these bacteria to mutate more readily to forms which are resistant to high levels of antibiotics. If further observation proves this to be consistently true, it may open the door to a new avenue of attack by way of these enzyme systems, which could have considerable therapeutic value in our campaign against the rising tide of drug-resistant infections.

620 W. 168th St. (32) (Dr. Lattimer).

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BACTERICIDAL ULTRAVIOLET RADIATION IN THE OPERATING ROOM

TWENTY-NINE-YEAR STUDY FOR CONTROL OF INFECTIONS

Deryl Hart, M.D., Durham, N. C.

Twenty-three years of experience with ultraviolet radiation in operating rooms has led to the conviction that this method of decontaminating the air is both effective and safe. There have been no serious or permanent deleterious effects on the eyes or skin of the operating room personnel, but there has been a striking reduction in postoperative complications and deaths attributable to infections. Fatal infections in clean operative wounds numbered 17 in the 5½ years preceding, and only 2 in the 5 years following, the adoption of ultraviolet radiation for this purpose. Records of 4,585 operations and of nearly 700 postoperative deaths during a 10½-year period were analyzed and showed a striking superiority of results in the operating rooms in which ultraviolet radiation was used. With properly chosen fixtures, properly placed, radiation at wave lengths from 253.7 to 290.0 mμ can be delivered with an intensity of 18 to 30 microwatts per square centimeter at the operative site. No evident permanent damage to personnel or patients has been detected during 23 years of daily use of such radiation in either the one original or the 15 now used operating rooms so equipped.

With the present widespread distribution of antibiotic-resistant staphylococci, the surgeons, hospitals, and patients, insofar as these organisms are concerned, are on the way back to where they were before the introduction of sulfonamides and antibiotics. However, we in the Duke Hospital have had no serious staphylococcic problem in the operating room since 1936, because, in our opinion, of the continuous use of ultraviolet radiation both during and between operations to control, in this area, the spread of bacteria by way of the air. The many recent reports in the literature listing a relatively high percentage of wounds infected with staphylococci, the universal concern over the present and potential dangers from these organisms, the apparent lack of information about the role of the air as a route of bacterial spread despite many reports in the literature, and the lack of knowledge in published work on the control of airborne infections by the use of ultraviolet radiation in the operating rooms bring this problem forcibly to our attention.

A recent article,[1] duplicating some of my published work, emphasizes the importance of carriers, their role in the contamination of the air, and the value of ultraviolet radiation in killing the bacteria in the air. The authors stated that its use between operations will cut down the bacteria count and allow each operation to start with bacteria-free air. However, it is also stated that, "Because of the deleterious effects of such rays on the eyes and skin of operating room personnel, it is not practicable to continually irradiate the entire operating room during an operation." This again emphasized the importance of presenting at this time a summary of experience with the use of ultraviolet radiation in the operating room at Duke Hospital during operative procedures for the past 23 years. The results obtained indicate that ultraviolet radiation and other measures used to limit the spread of bacteria by way of the air can go far toward solving the problem of bacterial contamination in clean operative wounds and eliminating the resultant so-called unexplained infections, which are usually with staphylococci.

Early Attempts to Control Unexplained Infections

During the period from July 21, 1930, to Jan. 15, 1936, *infections in these "clean" operative incisions*, predominantly with Staphylococcus aureus, were a continuous problem in the Duke Hospital and caused 17 deaths (1.3% of the patients having "clean" operations of the types analyzed). There was a definite tendency of fatal wound infections to occur in groups after "clean" operations performed without ultraviolet radiation. These occurred during the cooler months when there are periods of high staphylococcic and at times hemolytic streptococcic contamination of the upper respiratory tracts and the air of occupied areas. All of these infections were overwhelming, leaving no doubt as to the cause of death (meningitis, 7; proved septicemia, 5; suspected septicemia [with chills but without demonstrated positive blood culture], 2; extensive local invasion without proved positive blood culture, 3; and peritonitis, 2).[2] The following organisms were cultured from these patients (wound, spinal fluid, or blood), the numbers indicating the number of patients infected with the given organism: hemolytic Staphylococcus aureus, 9; Staphylococcus aureus, 5; Staphylococcus albus (meningitis), 2; gram-positive cocci in clumps (meningitis), 1; beta hemolytic streptococci, 4; gram-positive Diplococcus, 1;

From the Department of Surgery, Duke University School of Medicine.

Escherichia coli communior, 1. Mixed infections accounted for a total number of organisms greater than the number of patients infected. Each of the three patients having an orthopedic operation had a mixed infection, all with beta hemolytic streptococci, while two showed in addition Staph. aureus and one Escherichia coli. One patient having a laparotomy was infected (both wound and peritoneum) with Staph. aureus and beta hemolytic streptococci.

There were periodic exacerbations in the infection rate, and on two occasions (see table 1, 1933-1934 and 1935-1936) these were of sufficient severity to cause curtailment of operations in patients requiring extensive procedures, except in those with urgent conditions. At first we held the false impression that the rooms were primarily contaminated, and we attempted to rid them of bacteria by cleaning, but we were soon convinced that the occupants were the primary source of the offending organisms and that the room and air contaminants were derived from the occupants.

Table 1.—*Fatal Infections in Clean Operative Wounds, Duke Hospital, July 21, 1930, to Jan. 15, 1936 Without and Jan. 15, 1936, to Jan. 15, 1941, With Use of Ultraviolet Radiation*

Time, 7-21-30 to 1-15-36	No. of Days in Period	Radiation	No. of Deaths	Number of Deaths by Service and Date									
				Neurological		Thoracic		Orthopedic		General		Otolaryngologic	
				No.	Date	No.	Date	No.	Date	No.	Date	No.	Date
7-21-30 to 7-1-31	7	Without	2	1	3-27	0		0		1	3-21	0	
1931-1932	42	Without	2	1	12-22	0		1	2-2	0		0	
1932-1933	73	Without	2	1	11-1	0		0		1	1-12	0	
1933-1934	72	Without	6	1	1-26	3	11-15 12-6 12-28	1	12-22	1	1-16	0	
1934-1935		Without	2*	1*	10-31	1*	4-17	0		0		0	
1935 to 1-15-36	36	Without	3	1	9-16	1	10-15	1	10-22	0		0	
Subtotal, 5½ yr.	230	Without	17	6		5		3		3		0	
1-15-36 to 1-15-41		Without	2†	1†	4-20-36	0		0		0		1†	12-9-37
		With	0	0		0		0		0		0	
Subtotal, 5 yr.			2	1		0		0		0		1	
Total, 10½ yr.			19	7		5		3		3		1	

* Isolated occurrences.

† Isolated occurrences—infections probably limited by the use of ultraviolet radiation in most large clean operations.

While attempting to control this "old problem" we reevaluated every step of the "then generally accepted" aseptic technique.[2] At frequent intervals cultures were taken to check everything connected with the activity—sterile supplies, uniforms, gowns, masks, shoes, water, floors, walls, the Celotex ceiling in adjacent corridors, the hands of the personnel, and the skin of the patient, before preparation, after preparation, and at the end of the operative procedures. Cultures were also taken at frequent intervals to show any contamination of the incoming and outgoing air, the ventilating system, the air in the operating rooms, and the air of many other areas of the hospital.[2] Cultures of the upper respiratory tracts of personnel and patients were taken in an attempt to identify persistent carriers of pathogenic bacteria, with the objective of eliminating them from the operating room. This was done to reduce these infections and to determine the importance of carriers as a source of the air contamination and wound infections.[3]

Even though no serious defects were found, other than the frequent presence of carriers, the inadequacy of masks, and the constant air contamination, all techniques were made more rigid in every way and special emphasis was placed on the following additional requirements. All personnel, and not just the doctors and nurses, were given, each day, freshly laundered uniforms, free of pathogenic bacteria. Masks covering the mouth and nose were worn at all times by everyone entering the operating room area, and during extensive operative procedures double masks were worn. No talking was permitted during an operation. Extensive operations were performed only as first operations in the morning; if not urgent they were delayed until the summer or at least until cultures showed that the air contamination was low. Visitors were not permitted and personnel was kept to the minimum.

In addition, the Celotex ceiling in the corridors of the operating suite was replaced by plaster for more effective and easier cleaning; double doors were installed to limit air currents from the rest of the hospital; the operating rooms were ventilated with air under pressure and free of bacteria; they were painted frequently; and the walls and ceilings were washed weekly or more often. It soon became apparent that without any treatment other than ventilation, the air of the unoccupied room became almost free of settling bacteria within a few hours[3] and that in the rooms in which the floor was cleaned with an antiseptic solution, bacteria could not be stirred up in appreciable numbers by mechanical agitators such as electric fans.

Correlation of Wound Infections with Contaminants from Respiratory Tract

However, with human occupancy, the air contamination rose rapidly.[4] Furthermore, cultures showed that the air in the occupied operating rooms was the most heavily contaminated of any area in the hospital, that the contaminants were predominantly staphylococci, and that the degree of this contamination was directly related to the time of the year, the number of occupants, and the duration of occupancy. This contamination could be reduced by increasing the volume of washed and filtered air which was delivered to the room practically free of organisms.[5] Culture plates exposed to the outside air near the air intake on the roof of our hospital, located in the country with wooded surroundings, showed predominantly fungi and nonpathogenic bacteria and practically no staphylococci.[5a] It was shown, to our satisfaction, that this condition of air contamination in the operating room was brought about by occupancy and that these rooms were not otherwise unduly contaminated. It was further shown by cultures in over 30 hospitals in the United States that this was a widespread, if not universal, condition.[5a]

It was soon shown that the respiratory tract contamination of personnel and patients with Staph. aureus was lower in the summer months, with fewer carriers, and higher in the colder months, with a greater percentage of carriers.[6] There was a direct correlation between the respiratory tract contamination of the occupants, the air contamination of the occupied rooms, and the percentage of infections in clean wounds, all of which showed simultaneous peaks, with the infection rate at times reaching epidemic proportions (table 1).[7]

These studies have extended from 1930 to the present time, and as a result we at the hospital have introduced a number of additions to our aseptic precautions, some important and some of questionable value, while others have been found to be unnecessary and have been discontinued. After the development of a technique to control the spread of bacteria by way of the air, many of these requirements were relaxed, and there was no appreciable return to the previous high infection rate.

Addition of Ultraviolet Radiation to Aseptic Technique

During 1934 and 1935, preliminary studies[8] on the effect of bactericidal ultraviolet radiation on bacteria, fungi, and animal tissues were carried out. In 1936 bactericidal ultraviolet radiation was introduced into the operating room on an experimental basis, with the first operation on a patient performed in such a field on Jan. 15. Since that time, infections in clean wounds have been almost eliminated. During the next five years there were only two deaths from infections in clean wounds (craniotomy, April 20, 1936, and radical neck dissection, Dec. 9, 1937), but ultraviolet radiation was not used during either of these operations. However, the use of ultraviolet radiation in most of our extensive clean operations (2,600) during this time gave protection to patients for whom it was used and may have accounted for the absence of other fatal infections, particularly at the time of these deaths. For what might have occurred during periods of high air contamination, see the groupings of fatal infections in table 1. Not one of these 19 fatal infections followed operations performed in May, June, July, or August, when the air contamination is uniformly low; six occurred in a period of 72 days (the months of November, December, and January) during the colder season of 1933-1934 and three in a period of 36 days (Sept. 16 to Oct. 22) in the autumn of 1935 when the air contamination was demonstrated to be high.[9] (There are in the literature periodic reports on air contamination with pathogenic or at times "pyogenic" bacteria. These soon became lost in the mass of publications and have been ignored to a great extent.) Both of these severe epidemics caused us to restrict extensive operative procedures unless treatment was urgent, a step which probably saved additional patients from infection and possible death.

Each of the two fatalities in January, 1934, followed an operation at the time considered to be urgent. The first was for carcinoma of the breast, for which a physician member of the family wanted immediate operation despite the known danger from heavy contamination of the air in the operating room. The second patient had extremely severe trigeminal neuralgia (tic douloureux) and was operated on only after two previous admissions at five-day intervals with unsuccessful attempts to obtain relief by alcohol injections. After the fatalities in October, 1935, patients already admitted for extensive procedures such as thoracoplasties were discharged until the next summer or until completion of the installation of ultraviolet radiation in an operating room before having their operations.

Further analysis of table 1 shows that of the 17 deaths occurring before the use of ultraviolet radiation, only 2 were isolated occurrences separated from other such deaths by intervals of from five to nine months, while the other 15 showed some grouping tendency as to time but not as to service, except in the epidemic in 1933-1934 when there were three deaths on the thoracic service after extrapleural thoracoplasties. During the same period, however, there was one such death each on the general, orthopedic, and neurological services, demonstrating that these infections were caused by a general condition present in all operating rooms. It has been demonstrated[2] repeatedly that heavy air contamination is a general and not a local condition, rising and falling in all operating rooms simultaneously but not necessarily to the same degree. During periods with a high infection rate, there was an increase in the percentage of nose and throat carriers of Staph. aureus in the hospital population, at times up to 80%.[4a] It was also recognized that one constant, heavy nose and throat carrier of highly pathogenic bacteria can contaminate the air wherever he goes and is a constant hazard in the operating room.

During the years 1936 through 1946, various aspects of this study were presented before surgical groups and published in over 15 articles in several journals. Also, three scientific exhibits were shown, each of which received some recognition (first award at the Southern Medical Association meeting in 1936, honorable mention at the American Medical Association Annual Meeting in 1937, and the silver medal [second award] at the A. M. A. Annual Meeting in 1942, at which time comparative results covering five and one-half years without and five years with use of ultraviolet radiation were presented).[7a] This work as presented and published can be divided into the following four main divisions: (1) background investigations to determine the most common source and route of spread of the offending organisms; (2) procedures, including the use of ultraviolet radiation, for reducing the spread of these organisms by way of the air and limiting the seeding of the open wound; (3) safeguards necessary to protect patients and personnel exposed to ultraviolet radiation, making it possible to use this during the operation; and (4) results obtained by controlling the spread of bacteria by way of the air in the operating room.

Background Investigations.—In investigations of the source of the organisms and the route of spread the following points were brought out. There was continuous sedimentation of organisms, predominantly staphylococci from the air of the occupied room.[10] The incoming washed and filtered air supplied was relatively free of bacteria.[11] The bacterial flora in the outside air were predominantly fungi and nonpathogenic bacteria and were different from the flora in the air of the operating rooms, predominantly staphylococci, the group of organisms causing most of the wound infections.[4b] The concentration of the staphylococci in the air could be reduced by forced ventilation but not sufficiently to protect the wound from seeding with these organisms in sufficient numbers to cause suppuration in an appreciable percentage of patients.[12] Contamination of the air with staphylococci, with resultant seeding of the open wound, depended on the presence or recent presence of human beings in the area. With cessation of occupancy, the air contamination diminished rapidly. In the well-kept operating room and in the absence of human beings, air contamination could not, by mechanical agitation of the air, be built up to the former level attained during occupancy.[13]

The air of the operating room showed the highest level of staphylococcic contamination of any area in the hospital in which cultures were made, probable because of the greater concentration of people.[2] The concentration of this bacterial contamination of the air varied with the number of occupants,[5a] the time of year (which influenced the number of carriers),[13] and the percentage of carriers and the degree (type and number of the organisms) of contamination of their upper respiratory tracts.[2]

Control of Contamination.—Studies concerned with procedures for the control of air contamination showed the following facts. The average mask, even when two are worn, is inadequate to control air contamination.[14] Talking increases the build-up of the air contamination even when conventional masks are worn.[15] We were unable to develop a mask which was an efficient bacterial filter and which at the same time permitted free respiratory exchange.[15] The wearing of a helmet and use of suction beneath this to remove from the room the exhaled air containing bacteria was tried but found to be impractical.

Forced ventilation with clean air, by a process of dilution, reduced but did not, in the presence of continuing contamination from occupants, reduce adequately the level of this air contamination.[16] With occupancy, in the absence of ultraviolet radiation, the level of air contamination was built up so rapidly that little was accomplished by freeing the air of the operating room of most bacteria by (*a*) sedimentation followed by antiseptic mopping, requiring a longer period of closure without occupancy; (*b*) forced ventilation and a dilution process to supplement sedimentation, requiring a shorter period of closure without occupancy; or (*c*) sterilization of the air with ultraviolet radiation, a procedure which requires only a short period of unoccupied closure.[14a]

Direct exposure of staphylococci sprayed on a Petri dish of blood agar and exposed to ultraviolet radiation (24-30 microwatts per square centimeter) at the operative site for one to five minutes killed over 99% of the organisms, the variation in time required depending on the density of the inoculation and the presence or absence of clumping.[17] Many bacteria and fungi tested were killed with a suitable exposure to an intensity of ultraviolet radiation that could be used safely in the operating room.[18] With this intensity of radiation, 24-30 microwatts per square centimeter at the operative site in the occupied operating room during use, the viable colonies of organisms seeding on an exposed flat surface (Petri dish of blood agar) during one hour and surviving continued exposure were reduced in different parts of the room from 80 to about 95%, the variations depending on the type of installation and the intensity of distribution.[17] With this intensity of radiation at the operative site, the viable colonies of organisms seeding on a Petri dish of blood agar exposed in any part of the room and shielded from the radiation were reduced by over 75%, with use of a suitable intensity distribution. Most of the organisms in the air were killed in the air, apparently others were attenuated,[19] and most of the rest were killed after seeding on an exposed culture plate or other surface.[20]

Sterilization of the air within the air ducts is of value if air is being recirculated and the contaminating organisms are not removed by the air-conditioning system.[5a] However, such an installation will not give adequate protection, since it has been shown that the use of all fresh air, free of bacteria, did not reduce the bacterial content of air in the occupied operating room to a level which rendered it safe for all large operations.[11] Indirect radiation of only a part of the air in the operating room (with shading of the patient and of the head area of the personnel) was of some value but did not sufficiently reduce the number of viable organisms (only 30 to 50%) to afford adequate protection for the open wound. The radiation killed the organisms and did not inhibit their growth by its effect on the culture mediums.[4b]

Safeguards for Patient and Personnel.—The eyes of the personnel must be protected from direct radiation by shading (an eye shade is adequate) and should be protected from reflected radiation by glasses (any type of glass other than special glass made for transmission of ultraviolet rays is adequate). Otherwise, they may be burned to such a degree as to require local anesthesia. However, we have never detected any permanent damage to the cornea, lens, or conjunctiva, even though many of the personnel wear no glasses but only an eye shade, and some persons have been using ultraviolet radiation during operations for over 23 years.[17] The eyes of the patient must be protected by closure and covering with suitable material (a routine procedure employed by anesthetists during general anesthesia, but some form of protection must be used during the entire time of exposure to ultraviolet radiation).[17]

For frequent and long periods of exposure, the skin of the personnel and patient should be covered or shaded. However, an exposure of several hours is tolerated with only an erythema. There is considerable variation in the reaction, depending on the pigmentation of the individual person. No blisters have occurred and no evident permanent damage has been detected during the past 23 years of daily use in the one original to the 15 presently used operating rooms so equipped. There are many sun screen lotions that block varying percentages of the radiation. These can be used but should be suitably tested to determine whether they offer protection from radiation at 2,537 to 2,900 A. Some of these are quite effective, but they are not necessary, even though the circulating operating room personnel may not cover their arms and never cover their hands. These persons limit the total amount of exposure to which they are subjected by occupying the area of low intensity of radiation at the periphery of the room, when their duties permit.[14a] The exposed tissues (those of experimental animal and patient such as skin, peritoneum, muscle, brain, and spinal cord) have never, to our knowledge, been damaged seriously during the time necessary for our operative procedures, with use of an intensity of 18 to 30 microwatts per square centimeter at the operative site. With or without the use of ultraviolet radiation, it is desirable to protect exposed tissues from drying, and covering for this purpose also protects them from exposure to the radiation.[21]

Operating rooms with high ceilings permit the radiation units to be mounted at a greater distance above the patient and personnel. Such mountings require a larger output of radiation in order to obtain an intensity of 18 to 30 microwatts at the operative site. As compared to the units mounted at a lower level, these give a very high intensity in the upper air, where bacteria are carried by convection currents, a much lower intensity on the heads of the personnel, and a higher intensity on the floor and the periphery of the room. Such an intensity distribution gives a greater reduction in the bacterial contamination of the air of the entire room and at the same time simplifies the problem of protecting the personnel, by exposing their heads to a lower intensity and by making it easier to shade their eyes, since the rays come from a higher level.[12]

Table 2.—*Infections and Deaths from Infected Wounds After Clean Operations Performed With and Without Bactericidal Radiation, from July 21, 1930, to Jan. 16, 1941*

	Primary Incisions							
						Death from Infections		
	No. of Operations	Infections		Positive Cultures Obtained	No. of Deaths from Infection	% of Operations	% of Infections	Positive Cultures Obtained
		No.	%					
Without Radiation								
7-21-30 to 1-15-36	1,266				16	1.27		16
1-15-36 to 1-15-41		196	11.3	122	18	1.04	9.18	
	469*		↓‡	↓	2	0.43 ↓	↓	2
With Radiation								
1-15-36 to 1-15-41	2,460†	6	0.24	5	0	0	0	0
	Reopened Incisions§ (All Thoracoplasties)							
Without Radiation								
7-21-30 to 1-15-36	47	11	23.0 ↓	...	1	2.1 ↓	9.0 ↓	1
With Radiation								
1-15-36 to 1-15-41	140	9	6.4	8	0	0	0	0

*Rate of infection in this group was low, since most of the patients having operations likely to become infected were in the larger group in which ultraviolet radiation was used (2,460 primary incisions and 140 reopened wounds).

†The use of ultraviolet radiation was extended to operations which, by their nature, were contaminated, and there were in addition over 200 such operations not included in this chart.

‡The arrows indicate the comparative results without (above) and with ultraviolet radiation (below).

§Reopened wounds have a potential source of contamination from bacteria entering either during the previous operation or along the skin sutures between operations. Although there was great improvement after the use of ultraviolet radiation in these operations, the results were not as good as for the clean primary incisions.

Results in Reducing the Frequency and Severity of Infections

Results.—The results obtained by the use of ultraviolet radiation have been the elimination of deaths from unexplained infections in clean wounds (tables 1 and 2), a reduction in the infection rate in clean operations (table 3), fewer systemic and local reactions in patients having clean operations and not showing signs of gross suppuration (fig. 1 and 2),[7a] and a reduction in the number of infections and the severity of reactions in patients with grossly contaminated wounds. The condition of the wound as well as the amount and type of bacterial seeding influenced the infection rate, but in all types of wounds great improvement was brought about by the use of ultraviolet radiation to limit seeding of the wound and the exposed sterile field.

To obtain the statistics on results, the records of patients having 4,585 operations performed during the period of July 31, 1930, through Jan. 15, 1941, were analyzed. In these, the ratio of operations performed with to those without ultraviolet radiation was about 3:2 (table 2). Also, to be certain that no death from an infection in a clean wound (table 1) was missed, the record of every patient who died (almost 700) after a surgical operation (46,369) during this 10½-year period was analyzed according to the cause of death.

Table 3.—*Comparison of Postoperative Infection Rates With and Without Use of Ultraviolet Radiation for Different Types of Clean Operations, July 21, 1930, Through Jan. 15, 1941*

	Infection, %	
	Without Radiation	With Radiation
Thoracoplasty, first stage, and radical mastectomy	32.0	0.35
Orthopedic	16.5	0.74
Neurosurgical	9.0	0.22
Herniorrhaphy*	8.3*	0.00
Thyroidectomy	1.8	0.00
All operations	11.6	0.24

* Group includes inguinal, femoral, umbilical, and postoperative hernias.

Deaths from Unexplained Infections: When ultraviolet radiation was not used, the postoperative mortality from overwhelming infection after clean operations was 1.12% (19 deaths after 1,782 operations: craniotomy, 7; first stage thoracoplasty, 4; second stage thoracoplasty, 1; laparotomy in debilitated patients with ascites, 2; radical neck dissection, 1; radical mastectomy, 1; arthroplasty of hip, 1; fusion of knee, 1; and osteotomy of femur, 1). Of the group developing infections, 9.18% died (19 deaths after 207 infections) (table 2). In contrast to this, when ultraviolet radiation was used there was no death from infection after about 2,600 such operations (primary incisions and reopened wounds) performed between Jan. 15, 1936, and Jan. 15, 1941 (table 2).

Reduction in Percentage of Infections: When ultraviolet radiation was not used in the operating rooms at Duke Hospital, and despite all our efforts and precautions, the infection rate in clean cases was 11.6% (207 infections, 1,782 operations) (tables 2 and 3). Most of these were mild or moderate, but many were severe, as indicated by the mortality (9% of those infected) (table 2). One hundred twenty-two positive cultures were obtained from these wounds and recorded in the charts, with five patients showing mixed infections, giving a total of 127 organisms cultured.[7a] (Frequently, in the early cases, a culture was not taken if the infection was mild, and many of the orthopedic patients were in a cast until after discharge. The infection was found on return for an office visit but a culture was not taken.) Only 11 of these wounds showed an infection without staphylococci being present (streptococcus, 2 [1 also showing Esch. coli]; Esch. coli, 3; Bacillus proteus, 2; Bacillus subtilis, 2; Pseudomonas aeruginosa, 1; and gram-positive diplococcus, 1).[7a] The percentage of infections and their severity were influenced by many factors, including

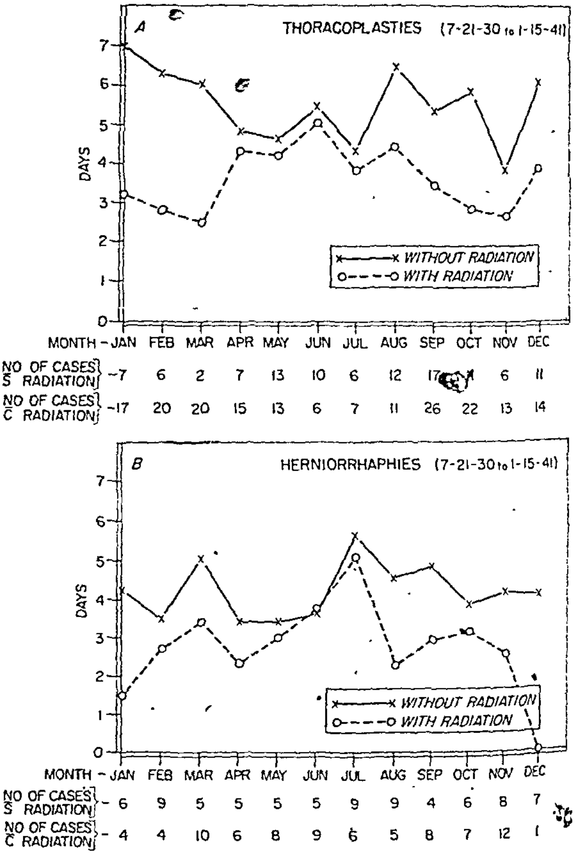

Fig. 1.—Average duration of temperature elevation for patients operated on each month with and without radiation. Greatest reduction brought about by use of ultraviolet radiation occurred during periods when air contamination was high, and least reduction occurred during periods when air contamination was low. During latter period, bacteria-laden perspiration not controlled by ultraviolet radiation was factor in wound contamination. Only once in these 24 recordings did average duration of temperature elevation for any irradiated group equal or exceed average for comparable nonirradiated group (hernia repairs during June by one-tenth of a day).

the susceptibility of the areas exposed (e. g., meninges), the magnitude of the operation, the trauma produced, the effectiveness of procedures for hemostasis, the presence of drains or other foreign material, the amount of motion in the wound after operation, the amount of bacterial inoculation, and, probably most important of all, the virulence of the seeded organisms versus the local and systemic resistance of the patient.

As contrasted to this, in patients with clean primary incisions in which ultraviolet radiation was used, the infection rate was only one-fourth of 1% (6 infections after 2,460 operations)[22] (tables 2 and 3) and most of the infections that occurred were mild.[23] In this group there was no death attributable to infection. Seven organisms (Staph. aureus, two; hemolytic Staph. aureus, two; Staph. albus, one; beta hemolytic streptococci, one; and organism undetermined, one) were obtained from five patients, the culture from one patient showing no growth while two patients had a mixed infection. After the 140 operations involving reopening of a wound, there were nine infections, with only eight identified organisms (Staph. aureus, three; hemolytic Staph. aureus, three; and Staph. albus, two); one patient's culture showed no growth (table 2).

Results in Reducing Local and Systemic Reactions

Fewer Systemic and Local Reactions.—As an additional method of evaluating ultraviolet radiation for air sterilization or, more correctly, "air sanitation" as an addition to aseptic technique, a comparison was made of the reactions of patients after operations performed in a field of ultraviolet radiation with the reactions of others having operations performed with use of a similar technique but without ultraviolet radiation.[21] As examples of this, the findings are given here for two types of operations—first stage thoracoplasty (extensive operations with severe trauma and poor hemostasis, with extensive areas of tissue exposed to seeding, and with much postoperative motion in the wound) and inguinal herniorrhaphy (less extensive operations with minimal trauma and good hemostasis, limited tissue exposed to seeding, and little postoperative motion in the wound). Every patient in each group operated on during the period July 21, 1930, through Jan. 15, 1941, was included.

In order that a totally objective analysis be obtained, the temperature charts, previously recorded by the nurses as part of their routine care of the patients, were analyzed, first, as to duration of any postoperative temperature elevation above the preoperative level (fig. 1) and, second, as to the percentage of postoperative temperature elevations above 37.5 C (99.5 F) recorded during eight days after operation (fig. 2).[24] The patients having each type of operation were further divided into 12 groups by month of operation to permit correlation of any improvement in the patient's reaction with the possible reduction in the level of bacterial contamination of the air of the operating room. The average duration of the postoperative temperature elevation above the preoperative level and the percentage of recordings showing some elevation were much less in the groups in which ultraviolet radiation had been used (fig. 1 and 2), the percentage of improvement showing some relationship to the improvement possible in the contamination of the air. That is to say, the greatest improvement occurred during the colder months, when the air contamination was high.

In these comparisons, the ultraviolet-irradiated groups showed only slight improvement over the nonirradiated groups in both duration and elevation of temperature during the warmer months when the air contamination was normally low, but bacteria-laden perspiration in the uncooled operating rooms in that period was profuse and a source of wound contamination not controlled by ultraviolet radiation. Cultures from the skin or gown, wet with perspiration, at times showed innumerable colonies,[24] most frequently of Staph. albus. These organisms were, in general, only mildly pathogenic but were capable of producing a local and systemic reaction usually short of visible evidence of sup-

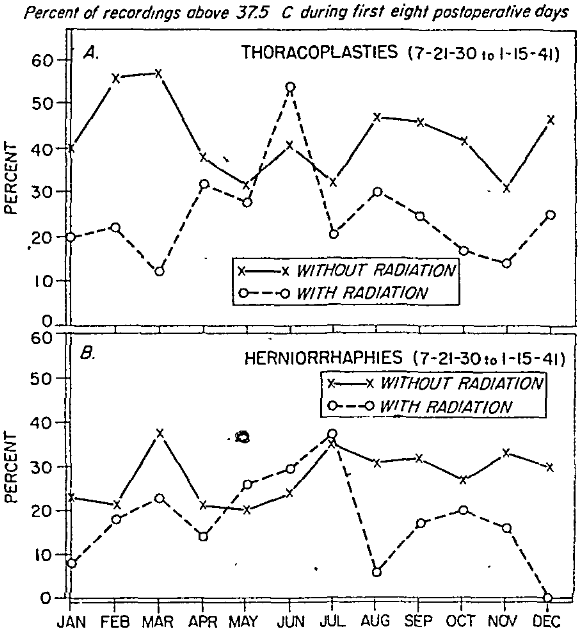

Fig. 2.—Comparison of temperature reactions after operations performed with and without bactericidal radiation. For each group of patients every temperature recording above 37.5 C was tabulated and plotted as percentage of total number of temperatures taken in group during first eight days after operation (4, 8, and 12 o'clock, day and night). For patients undergoing thoracoplasties, there was only one month (June) and for those undergoing herniorrhaphies three months (May, June, and July) in which percentage of temperature elevations above 37.5 C (99.5 F) in irradiated patients was slightly greater than percentage of each elevation in nonirradiated groups. All of these were in warmer months, when contaminated perspiration in uncooled operating rooms of that time may have been more serious route of wound inoculation than air, with its low contamination with pathogenic bacteria.

puration. However, if either the patient or one of the staff has a virulent skin contaminant, this may be a source of serious infection.

Improvement in Grossly Contaminated Wounds.—While we do not as yet have statistics for proof, the composite clinical impression of the surgeons is that, even for the patients having an operation which necessarily gives a contaminated wound (e. g., open resections of the gastrointestinal tract and pneumonectomy), the number and severity of infections and other local and systemic reactions have been reduced greatly by the use of ultraviolet radiation. The general, thoracic, neurological, and orthopedic surgeons at Duke Hospital now use ultraviolet radiation routinely in such operations, believing it desirable not to mix the flora already present within the patient with exogenous flora from the contaminated air. The latter, predominantly staphylococci, either alone or in combination, are probably, in most instances, more pathogenic for the patient and, therefore, liable to induce a greater reaction.

Comment

To those of us who went through the trying experiences with infections at Duke Hospital from 1930 to 1936, the results obtained by the use of ultraviolet radiation have been nothing short of miraculous. Each surgeon who has used this radiation has done so by his own request, and whenever it has been introduced on any service at Duke Hospital, the improvement in results has been immediate and continuous. No member of the staff who has once started using this addition to aseptic technique has given it up, and we now have 15 operating rooms so protected.

Within the past few months, I have been asked repeatedly why, if we still use ultraviolet radiation, no recent reports have been given in the literature. Others have told me that in conversations the statement has been made to them that we must have given it up since we no longer publish reports on the subject. The explanation for our silence is that after the presentations listed, the last of which came out in 1946, it was my opinion that our findings had been presented adequately and that the need for, the effectiveness of, and the safety of ultraviolet radiation as a part of aseptic technique had been proved. Furthermore, it was our opinion that if members of the profession chose to accept the heavy seeding with viable pathogenic bacteria sedimenting from the contaminated air and then to attempt to control the growth of these bacteria by the use of the newly introduced "miracle drugs" rather than to kill the bacteria in the air before they entered the wound, little would be accomplished by further presentations of the same or supplementary data.

Most members of the profession consulted at that time did not consider the air to be an important route of bacterial spread, doubted the value of ultraviolet radiation in the operating room, and considered its use during the operation to be, at the least, a nuisance, requiring for the personnel protection which might be mildly annoying, and, at the most, a handicap in operating and a hazard to themselves, the other personnel, and the patient. they believed, furthermore, that, with the new chemicals and antibiotics available to control infections, such precautions were unnecessary.

However, for our own work in the Duke Hospital, all the surgeons on the general, thoracic, neurological, and orthopedic services, who perform most of the clean extensive operations in which there is most likelihood of infection from contamination in the air, have continued to use ultraviolet radiation in the operating room routinely. Having seen the great reduction in the adverse postoperative reactions brought about by controlling this route of bacterial dissemination and seeding of the clean wounds, they have extended its use to all extensive procedures, including those in which there is gros contamination. It has always been our opinion tha keeping pathogenic bacteria out of a clean woun is preferable to trying to control their growth or t kill them after they enter, a subject we conside closed to argument. With the present widesprea distribution of antibiotic-resistant staphylococc prevention of such *contamination* is now all th more important.

Since our last publication, infections in clea undrained wounds at Duke Hospital have bee extremely rare. When occurring, they have in mos cases been mild, and fatalities from such infection have been almost, if not entirely, nonexistent. (I d not know of a single such death in a case in whic ultraviolet radiation has been used, but all record are being carefully reviewed with regard to this.

It is suggested that anyone having a problem with infections in clean operative wounds expose a Petri dish of blood agar near the operativ site during those procedures in which infectio is most likely to occur and then incubate and determine the bacteria type settling from the ai When a wound becomes infected, the organisms obtained from the wound should be compared with those recovered from the air on the culture plate to see if they are the same. An operating room should be equipped with a suitable intensity distribution of ultraviolet radiation and kept protected continuously with radiation, and the bacteria settling from the air during an operation and near the operative site should be cultured and compared again with similar cultures taken under similar conditions but without the use of this radiation. The infection rate for similar operations performed by the same team, at the same time of year, with and without bactericidal radiation, should be compared. With this information, the decision as to the source of clean wound contamination and the value of ultraviolet radiation can be fairly made.

Summary

In the Duke Hospital so-called unexplained infections in clean operative wounds not only have been explained but have been eliminated, to a great extent, by a variety of measures aimed at limiting the contamination of the air with pathogenic bacteria, and by the use of ultraviolet radiation to kill the remaining bacteria that inevitably get into the air and, by sedimentation, onto exposed surfaces. We have thus reduced greatly the spread of viable pathogenic organisms in the operating rooms by way of the air, regardless of their origin.

We consider the air route of spread to be the greatest factor in the seeding of clean operative wounds and exposed sterile supplies with pathogenic bacteria and therefore to be responsible for most of the so-called unexplained infections in clean operative wounds today.

Despite the high rate of operative wound infections reported, the universal contamination of the air in occupied closed areas and the effectiveness, safety, and ease of use of ultraviolet radiation in the operating room, the air in the operating room is almost universally ignored, except for two procedures. The first is the use of inadequate masks, which produce a false sense of security, since they may stop the large droplets but not the droplet nuclei of bacteria which contaminate the air. Second is the use of air conditioning, which does not reduce adequately the contamination of the air in the operating room. Adopted for cooling and humidity control, air conditioning eliminates or reduces the amount of bacteria-laden perspiration in the hotter months and provides at all times better ventilation with large quantities of air which should be relatively free of bacteria, thus reducing the concentration of pathogenic bacteria given off by the occupants of the room and floating in the air. It should be evident that control of bacterial spread by way of the air will, during the operation, protect the open wounds from heavy inoculation with exogenous pathogenic bacteria floating in the air, regardless of their source (respiratory tract; contaminated room; shoes, linens, and blankets; air from other areas; or air delivered in a contaminated condition from the ventilating system). Since contact inoculations have been eliminated, to a great extent, sterilization of the air will close the last big gap in our aseptic technique.

Before 1936 we were unable to prevent a high percentage of infections, predominantly with staphylococci, in clean operative wounds .At times, the number of infections was so great and they were so severe that limitations were placed on accepting patients for extensive clean operations. In contrast to this experience, since 1936, when we began the use of ultraviolet radiation to control the spread of airborne bacteria, such operating room infections have been all but eliminated. We now have 15 operating rooms equipped with bactericidal ultraviolet radiation in the Duke Hospital.

On the basis of our experience in the continuous control of these infections over a period of 23 years on a large surgical service, without permanent or serious injury to personnel or patient by the use of this agent, we again recommend that bactericidal ultraviolet radiation be used continuously as an addition to aseptic operating room technique. By this means, we have controlled the spread of pathogenic bacteria by way of the air with the result that we have eliminated most of the so-called unexplained infections and have kept under control the antibiotic-resistant staphylococci and other bacteria in the operating rooms in the Duke Hospital.

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MASCULINIZATION OF FEMALE FETUS DUE TO USE OF ORALLY GIVEN PROGESTINS

Lawson Wilkins, M.D., Baltimore

A markedly masculinized female infant is readily mistaken for a hypospadic male or for a normal male with simple cryptorchism. This congenital condition is sometimes caused by virilizing adrenal hyperplasia, but data here presented show that it has also frequently resulted from administration of progestins to mothers in treating habitual or threatened abortion. Seventy cases of fetal masculinization of female infants associated with the oral administration of progestins to their mothers are analyzed. Thirty-one followed the use of 17-α-ethinyltestosterone, and 35 followed the use of 17-α-ethinyl-19-nortestosterone. In 25 cases the mothers were given estrogens with the progestins in order that the estrogen might offset the virilizing effect of the progestin, but the evidence showed that the estrogens did not prevent fetal masculinization. These data do not argue against the use of progesterone, for the progestins concerned in all cases were synthetic.

Female pseudohermaphroditism due to congenital virilizing adrenal hyperplasia is a well-known condition.[1] The abnormality of sex differentiation is confined to partial masculinization of the external genitalia, while the ovaries are normal and the genital ducts are differentiated along the normal female pattern, forming vagina, uterus, and fallopian tubes. Embryonic masculinization of the external genitalia results in an enlarged phallus, which may or may not be associated with varying degrees of fusion of the labioscrotal folds. If little or no fusion occurs, separate vaginal and urethral orifices are visible. Fusion results in the formation of a urogenital sinus whose opening is either funnel-shaped or slit-like or in the form of a small meatus at the base or even on the shaft or tip of the phallus. Such a female infant may be readily mistaken for a hypospadic male or even a normal male infant with simple cryptorchism.

Fetal masculinization of the external genitalia with identical anatomic findings occurs also in females who do not have any adrenal abnormality. Unlike patients with the adrenogenital syndrome, these infants do not have elevated levels of urinary 17-ketosteroids and, as they grow older, they do not show progressive virilization with precocious growth of sexual hair and accelerated growth and osseous development. At puberty normal feminization, with menstruation and ovulation, occurs.

The diagnosis of female pseudohermaphroditism not due to adrenal abnormality depends on demonstration in the buccal smear of the "chromatin-positive" type of nuclei which are found in normal females[2] and on the finding of normal levels of 17-ketosteroids in the urine. When a urogenital sinus is present, it is generally advisable to perform a urethroscopic examination to demonstrate the communicating vagina and to observe the cervix. With high degrees of masculinization it may b advisable to perform an exploratory laparotomy t exclude the possibility of true hermaphroditism with mixed testes and ovaries, which is an exceedingly rare condition.

In 1958 my colleagues and I[2b] reported 17 instances of nonadrenal female pseudohermaphroditism, 12 of which occurred in infants born o mothers who, because of habitual or threatened abortions, had received 17-α-ethinyltestosterone (ethisterone, pregneninolone), a synthetic, orally given progestin, during gestation. This compound ha

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From the Division of Pediatric Endocrinology, Department of Pediatrics, Johns Hopkins University School of Medicine.

been used for about 15 years under such trade names as Progestoral, Pranone, and Lutocylol. In this paper warning was given that a newer progestin, 17-α-ethinyl-19-nortestosterone, marketed as Norlutin, might have even greater masculinizing effects on the fetus.

Report of Cases

Seventy cases of fetal masculinization of female infants associated with the oral administration of progestins to their mothers are presented. All of these cases fulfilled the diagnostic criteria discussed above. Twenty-three of these patients were studied by myself in the pediatric endocrine clinic of the Harriet Lane Home. Seventeen cases were reported on by Grumbach and co-authors,[3] and one case each by Moncrieff,[4] Hayles and Nolan,[5] and Reilly and co-authors.[6] Jacobson[7] observed 17 cases in his obstetric practice. The rest of the cases were brought to my attention by other colleagues. In visiting various clinics throughout the United States I have heard of many more cases, but I do not have sufficiently accurate data to include them in this study.

Table 1.—*Masculinized Females Whose Mothers Received 17-α-ethinyltestosterone (Ethisterone) During Gestation*

						Drugs Given			
						17-α-Ethinyltestosterone			
Observer	Case Identification	Birth, Yr.	Age Studied	Phallus	Fusion*	Daily Dose, Mg.	Period of Gestation, Wk.	Other Steroids	Maternal Virilization†
Wilkins	1	1957	1 day	+	++++	200	4-22	[illegible] dose	...
	2	1955	2 day	++	+++	50-200	4-35	[illegible]	...
	3	1955	15 mo.	+	+++	150-200	6-39	[illegible] days	...
	4	1957	1 day	+	+++	200	4-26	17-α-hydroxprogesterone, 250 mg./wk.	...
	5	1957	4½ mo.	++	+++	200	8-39	...	...
	6	1959	1½ mo.	+	+++	60	3-26	...	
	7	1953	4¾ yr.	++	++	30	10-22	[illegible]	...
	8	1957	7 day	+	++	40	5-39	[illegible]	...
	9	1952	4¾ yr.	++	+	100-80	4-39	[illegible]	...
	10	1953	3¼ yr.	++	+	30	8-26	...	
	11	1950	7 day	++	+	30	10-39	Ethinylestradiol, 0.1 mg.	...
	12	1957	2 yr.	+	+	40	6-35	Diethylstilbestrol, unknown	...
	13	1950	7 yr.	++	0	...	6-30	Diethylstilbestrol, unknown	...
	14	1951	2 yr.	++	0	40	5-39	Diethylstilbestrol, unknown	...
	15	1953	4 yr.	+	0	20-40	7-39	Diethylstilbestrol, 100 mg.	...
	16	1953	7 yr.	++	0	30	8-35	...	
	17	1952	6 yr.	++	0	60	14-35	...	
	18	1958	1½ mo.	+	0	20	16-8	...	
Grumbach and others[3]	H.N.	1953	3 yr.	++	+++	200	2-22	Diethylstilbestrol, 5-75 mg.	...
	S.H.	1954	4 yr.	++	+++	200-250	4-33	...	...
	D.F.	1951	8 yr.	++	+++	...	7-38	...	V
	B.N.	1957	Stillbirth	++	++++	30	11-15	...	...
	S.S.	1958	10 mo.	+	+++	100-50	4-36	...	...
	D.McC.	1950	5 yr.	++	++	30	6-32	...	...
	L.W.	1952	5 yr.	++	0	50	8-12	...	A H
	B.S.	1958	1 day	+	0	45	16-28	...	...
Bongiovanni and Eberlein	1	...	...	++	+++	10	1-28	Progesterone, 50-100 mg./wk.	...
	2	...	...	++	0	30-10	14-35	Conjugated equine estrogens (Premarin), 5 mg.	
	...	...	...	...	...	...	...		
	3	1958	2½ mo.	++	+++	100-200	10-39	...	...
	4	1959	2 mo.	++	+++	50-100	6-39	Diethylstilbestrol, 25-50 mg.	...
Foxworthy		1957	...	++	0	40	4-17	Ethinylestradiol, 0.04 mg.	...
Hayles and Nolan[5]	2	1953	3 yr.	+	0	20-60	4-37	Conjugated equine estrogens, 2.5 mg.	...
Reilly and others[6]	7	1957	1 day	+	0	120-240	18-39	...	...
Moncrieff[4]	2	1957	9 day	++	++	60	6-39	Ethinylestradiol, 0.06 mg.	...

* Labioscrotal fusion: ++++ urogenital sinus opening on shaft or tip of phallus; +++ urogenital sinus with small meatus at base of phallus; ++ urogenital sinus with slit-like or funnel-shaped orifice; + slight posterior fusion, separate vaginal and urethal orifices.
† Maternal virilization: V = deepening of voice; H = hirsutism of face; A = acne; C = clitoral enlargement.

Table 1 lists 34 cases associated with the use of 17-α-ethinyltestosterone. Table 2 shows 35 cases in which Norlutin, 17-α-ethinyl-19-nortestosterone, had been given and one case in which Enovid (norethynodrel and ethinylestradiol 3-methyl ether) had been used. The phallic enlargement, designated "+" or "++" (tables 1 and 2), consisted of hypertrophy of the corpus and glans and was not merely hyperplasia of the prepuce. In general, the degree of hypertrophy was considerably less than that usually seen in cases of congenital virilizing hyperplasia of the adrenal. In some cases the organ was not sufficiently conspicuous to make amputation advisable. Some of the infants having high degrees of labioscrotal fusion (for designation of the degrees of fusion see footnotes to tables 1 and 2) had been mistaken for males at birth and had been raised as such. With both 17-α-ethinyltestosterone and Norlutin, fusions occurred only when administration of the drug was begun before the 12th week of gestation. Phallic enlargement can result when androgenic activity is exerted over a sufficient period at any time during fetal or postnatal life.

The 34 cases of masculinization associated with administration of 17-α-ethinyltestosterone were observed in infants born between the years 1950 and 1959; the 36 infants whose mothers had been given Norlutin or Enovid were all born in 1958 and 1959. Although the daily doses of 17-α-ethinyltestosterone ranged from 20 to 250 mg., seven of the mothers had received 100 to 250 mg. daily. The doses of Norlutin ranged from 10 to 40 mg. per day, and high degrees of masculinization were observed with doses as small as 15 mg. daily. It is of particular interest that Jacobson[7] found that of 53 female infants born to mothers to whom he had given Norlutin in doses between 10 and 40 mg. per day, 17 showed masculinization, some in high degrees. Two mothers who had received 17-α-ethinyltestosterone, three who had received Norlutin, and one who had received Enovid showed mild androgenic manifestations, such as deepening of the voice, facial hair, and acne, which disappeared after the termination of pregnancy.

These findings indicate that (1) high degrees of masculinization occur with much smaller doses of Norlutin than of 17-α-ethinyltestosterone and (2) there has been a higher incidence of masculinized infants born to mothers who have received Norlutin than to those given 17-α-ethinyltestosterone.

Mode of Action

As shown in table 3, in 70 of 101 cases of nonadrenal female pseudohermaphroditism reported the mother had received one of the orally given progestins during gestation and in 15 cases testosterone or one of its androgenic derivatives. The probable mode of action of the orally given synthetic progestins has been discussed in previous communications.[8]

TABLE 2.—*Masculinized Females Whose Mothers Received Norlutin (17-α-ethinyl-19-nortestosterone) or Enovid (Norethynodrel and Ethinylestadriol 3-methyl Ether) During Gestation*

						Drugs Given			
						Norlutin			
Observer	Case Identification	Birth, Yr.	Age Studied	Phallus	Fusion*	Daily Dose, Mg.	Period of Gestation, Wk.	Other Steroids	Maternal Virilization†
Wilkins	1	1958	5 day	+	+++	5-20	6-30	...	...
	2	1958	12 mo.	+	+++	20-35	3-39	...	...
	3	1958	1 day	++	+	15	10-30	...	...
	4	1958	3½ mo.	++	+	10	7-35	Diethylstilbestrol	...
	5	1958	6 mo.	++	0	30-20	15-39	...	...
Grumbach and others[3]	A.R.	1958	4 day	+	+++	40-20	7-27	...	...
	S.B.	1959	1 day	++	+++	15- 5	8-29	Diethylstilbestrol, 75 mg.	...
	B.W.	1958	1 day	++	+++	10-15	7-29	Diethylstilbestrol, 25-175 mg.	V H
	S.B.1	1959	13 day	+	+++	15-40-20	5-35	Conjugated equine estrogens	V H
	B.B.	1959	6 day	+	++	15	7-24	...	...
	G.L.	1957	4 day	++	+	15- 5	10-36	...	...
	T.J.	1959	2 mo.	++	+	40-20	6-28	...	...
	D.W.	1958	2 day	++	0	10	15-31	17-α-hydroxyprogesterone, 250-500 mg./wk.	V
	S.M.	1957	5 mo.	++	0	10	19-28	Diethylstilbestrol	...
Bongiovanni	1	1958	...	+	++	10-15	1-39	Diethylstilbestrol, 75-100 mg.	...
	1	1958	...	+	+	10-20	10-39	Diethylstilbestrol, 25 mg.	...
D. W. Smith	1	1958	...	++	0	20	14-33	Progesterone (IM), 50 mg.	...
Valentine	1	1958	...	+	0	10	5-39	...	...
Jacobson	17 of 53 masculinized female infants born to mothers receiving Norlutin 10-40 mg./day.								
Grumbach	1	1958	1¼ mo.	++	++	Enovid, 10 mg.	6-38	... ...	V H A

* Labioscrotal fusion: ++++ urogenital sinus opening on shaft or tip of phallus; +++ urogenital sinus with small meatus at base of phallus; ++ single slit-like or funnel-shaped orifice; + slight posterior fusion, separate vaginal and urethral orifices.

† Maternal virilization: V = deepening of voice; H = hirsutism of face; A = acne; C = clitoral enlargement.

It has been demonstrated that testosterone and its known androgenic analogs, when administered to pregnant animals, can bring about masculinization of the fetus; in addition, 14 cases of fetal masculinization due to administration of these drugs to pregnant women have been reported.[9] It is probable that fetal masculinization may result from doses so small that they do not cause androgenic manifestations in the mothers or in normal adults. This may be due to increased sensitivity of the fetal end-organs or to impairment of the degradation and disposal of these steroids by the fetus. We have studied a highly virilized female infant from Vancouver, British Columbia, whose mother, from the 8th to the 39th week of pregnancy, had received one pill daily containing only 3 mg. of 17-methyltestosterone and 0.01 mg. of 17-ethinylestradiol. Moncrieff [4] has reported on two patients whose mothers received two or three of these same pills daily (6 or 9 mg. of methyltestosterone).

17-α-ethinyltestosterone, Norlutin, and Enovid are chemically similar to 17-methyltestosterone, since all have the 17-OH group in the beta position. 17-α-ethinyltestosterone has been shown to have androgenic effects in animals. In 1942 Courrier and Jost [10] reported that its administration to pregnant rabbits caused masculinization of the female fetus. This was confirmed in 1947 by Jost [11] in additional experiments. Recently, Revesz and co-workers[12] have brought about fetal masculinization by administration of 0.5 mg. of Norlutin daily and of 0.25 mg. of medroxyprogesterone (6-methyl-17-acetoxy-progesterone) to pregnant rats, although daily doses of 200 mg. of progesterone had no masculinizing effects. It would seem that both 17-α-ethinyltestosterone and Norlutin, and probably Enovid, are androgenic. Norlutin seems to be much more androgenic than 17-α-ethinyltestosterone. Even though bioassays may show that these compounds are relatively weak in terms of their androgenic effects on adults, they are sufficiently potent when they cross the placenta to masculinize the relatively sensitive end-organs of the developing fetus. It is no longer necessary to assume that the mothers who give birth to masculinized females metabolize these steroids abnormally. The fact that not all the offspring of mothers who received these drugs during gestation are affected may be due to differences in placental transmission or fetal sensitivity.

The question whether estrogens and progesterone can play a role in fetal masculinization has been raised. It will be noted that in 16 of our cases in which 17-α-ethinyltestosterone was given and in 9 in which Norlutin was used, the mothers received in addition either diethylstilbestrol (Stilbestrol), conjugated equine estrogens (Premarin), or 17-α-hydroxyprogesterone caproate. In some cases the diethylstilbestrol was given in very large doses. These substances certainly did not prevent fetal masculinization. Bongiovanni and co-authors,[13] reported on four masculinized female infants whose mothers had received diethylstilbestrol in doses of 5 to 75 mg. per day. In a previous communication we[2b] reported on two cases in which the mothers had been given only progesterone intramuscularly, over short periods of time, in doses which did not seem excessive. In addition, we have now observed four masculinized female infants whose mothers had received no medication of any kind, and there are similar cases in the literature.

There is no evidence that musculinization of the fetus is due to a direct androgenic action of progesterone itself.[12] Jost[14] recently restudied purified progesterone and could demonstrate no androgenic activity. One may postulate, however, that mothers of masculinized infants who have received no treatment and those treated with progesterone may metabolize either endogenous or exogenous progesterone abnormally to form androgens, since progesterone may be a precursor of both androgens and corticosteroids. The mothers who received diethylstilbestrol alone may belong to this group of abnormal progesterone metabolizers. On the other hand, Bongiovanni and co-workers'[13] suggestion that diethylstilbestrol may stimulate the fetal adrenal to increase the output of androgens cannot be refuted. Further work needs to be done in this field.

Comment

I am not qualified to discuss the debatable efficacy of progestational steroids or estrogenic compounds in the prevention of abortions. If they are valuable and necessary, the ones which are least likely to cause fetal masculinization should be used. There is no excuse for giving a known androgenic steroid, such as methyltestosterone, even in small doses. There is no valid reason to blame the administration of progesterone, the natural hormone of pregnancy, for the masculinization of female infants, although occasionally there may be a mother who metabolizes progesterone abnormally. On the other hand, the synthetic progestins given orally are not natural hormones of the body and have weakly androgenic as well as progestational action. During the past year or two, Norlutin has caused fetal masculinization with sufficient frequency to preclude its use or advertisement as a safe hormone to be taken during pregnancy. Although the older compound 17-α-ethinyltestosterone has caused masculinization comparatively infrequently, it should also be considered potentially hazardous to the fetus.

It is most important for the obstetrician, pediatrician, and family physician to recognize that nonadrenal female pseudohermaphroditism does occur, especially when motners have been treated with the orally given synthetic progestins under discussion. These infants can readily be mistaken for males. If they are raised as males, the physician will be greatly embarrassed when they feminize and menstruate at puberty. Whenever the external genitalia have an ambiguous appearance or when an infant appears to be a hypospadic male or even a normal male with impalpable testes, the possibility of female pseudohermaphroditism should be considered and excluded. The nuclear chromatin pattern of the buccal smear should be studied.[2a] If it is chromatin-positive, the urinary 17-ketosteroid levels should be measured, to determine whether or not virilizing adrenal hyperplasia is present. Nonadrenal female pseudohermaphrodites should always be raised as girls. One can reassure the parents that they will develop as normal girls and mature into normal, fertile women. No hormonal therapy is required. If there is no labioscrotal fusion, no surgical correction is necessary unless the phallus is so large that its removal seems advisable for cosmetic or psychological reasons. Labioscrotal fusion, when present, should be corrected by an operation such as that described by Jones[15] in early infancy or certainly before the age of 2 or 3 years.

TABLE 3.—*Nonadrenal Masculinization of Female Infants*

	Number of Infants Masculinized				
Drug Given Mother	Studied by Wilkins	Studied by Others	Total	Daily Dose, Mg.	Mothers Virilized
Ethinyltestosterone	18	16	34	20-200	2
Norlutin	5	30	35	10-40	3
Enovid	0	1	1	10	1
Testosterone and known androgens	1	14*	15	3-10	+(?)
Progesterone (IM)	2	0	2	50-100(?)	...
Diethylstilbestrol	0	4†	4	5-75	...
None	4	6‡	10	...	2
Total	30	71	101		

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* Grumbach and Ducharme.[9]
† Bongiovanni and others.[13]
‡ Wilkins and others.[2b]

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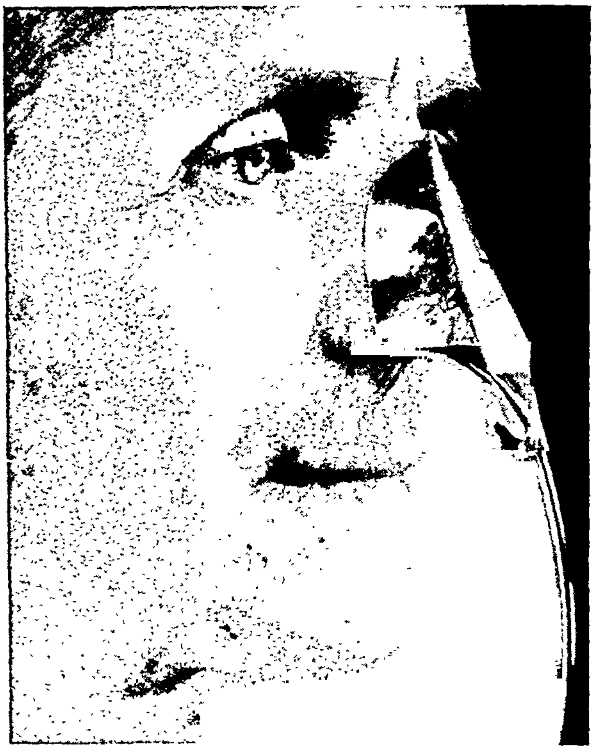
CLINICAL NOTES

NEW METHOD FOR HOLDING NASAL TUBES IN POSITION

Edward J. Hill, M.D., Detroit

A problem common to most patients subjected to nasal intubation for the purpose of either suction or long-time feeding is the difficulty involved in maintaining the tube in a fixed position. The usual method of fixation is the use of adhesive tape for adhering the tube to the nose, the cheek, or the forehead. This method is far from ideal, because adhesive tape quickly loses its effectiveness, becoming stretched or loosened by perspiration, thereby allowing the tube to move in and out as the patient swallows. This motion and the obvious pressure against the alar rim of the nose creates an unpleasant irritation or cellulitis which eventually leads to ulceration if the condition is not corrected.



Holder for nasal tube of thin malleable aluminum, approximately 0.005 mm. in thickness, molded to nose by digital pressure.

A new tube holder has been developed which is easily affixed to the nose, with no discomfort to the patient. It is constructed of a thin malleable aluminum, approximately 0.005 mm. in thickness, and is easily molded to the nose by digital pressure; it may be bent in any direction whatsoever. The holder projects below the tip of the nose to secure the nasal tube clear of the nasal rim, thereby eliminating the rubbing and irritation produced by the old method of securing the tube (see figure). The thinness and type of material allows it to be cut, if necessary, by the ordinary bandage scissors. The holder, or splint, has on one surface a nontoxic, nonirritative adhesive which keeps it firmly in position and allows the projection below the tip of the nose to grasp the nasal tube securely. This splint is designed to fit the nose snugly and is as easy to apply as ordinary adhesive tape. Its outstanding feature is that it may be firmly secured without rubbing or irritation to the nose. These splints have been designed to fit both adults and children.

1553 Woodward Ave. (26).

INTERNAL DRAINAGE OF ACUTE PSEUDOCYST OF THE PANCREAS

Capt. Wil B. Nelp
and
Lieut. Col. Strother B. Marshall, (MC), U. S. A. F.

Although pancreatitis is not an uncommon precursor of pancreatic pseudocyst, it is usually the chronic or relapsing form of the disease which gives rise to cyst formation. It is rare for an initial attack of acute necrotizing pancreatitis to lead to the development of pseudocyst. In the following case the rapid development of a large pseudocyst in the wake of an initial attack of severe necrotizing pancreatitis produced almost complete gastric obstruction and required early surgical intervention.

Report of a Case

A 21-year-old man was brought to the hospital by ambulance. Forty-eight hours prior to admission he had had sudden cramping epigastric pain and nausea, which soon subsided. Five hours prior to admission he again developed sudden severe epigastric pain and a burning sensation, with vomiting. There was radiation of the pain to the middle of the back.

His personal and family histories were unrevealing except for excellent general health. There was no history of gastrointestinal complaints, trauma, or operation. He did not drink alcoholic beverages.

Physical examination on admission revealed that the patient was well developed, well nourished, and in acute distress. He was pale, perspiring, and complaining of severe epigastric and back pain. His temperature was 97.4 F (36.3 C) pulse rate 92 per minute, blood pressure 124/80 mm. Hg, and respirations 16 per minute.

Skin and conjunctiva were clear. The abdomen was symmetrical and slightly distended. There were board-like rigidity and exquisite epigastric, flank, and middle back tenderness, and bowel sounds were absent.

Initial laboratory data showed a white blood cell count of 25,000 per cubic millimeter, with a marked shift to the left. The hemoglobin concentration was 18.4 Gm. per 100 cc., with results of urinalysis normal. A roentgenogram of the abdomen showed no free air, moderate distention of the large intestine, and a distended jejunal "sentinel loop" in the left upper quadrant. Serum amylase level was 546 Somogyi units (normal: 80-150 units).

A diagnosis of acute pancreatitis was made. Gastric suction was instituted and atropine, analgesics, and sedation were given, with fluids administered intravenously. Therapy with penicillin and streptomycin was started. There was some measure of relief, but pain was markedly increased by motion or when suction was discontinued for brief intervals. Oral feeding produced severe pain. During the first week the foregoing therapy was continued. His temperature intermittently rose to 101 F (38.3 C). The fever then abated and there was softening of the lower abdomen, but persistent epigastric guarding and tenderness remained. From the 7th to the 10th hospital day epigastric fulness became exaggerated and a rounded, smooth, tender mass could be outlined with some difficulty. On the 11th hospital day feedings were started orally but were poorly tolerated because of pain and vomiting.

On the 16th hospital day intravenous alimentation was resumed. The serum amylase level was still 312 units; the white blood cell count ranged between 10,000 and 20,000 per cubic millimeter. Serum protein, bilirubin, and electrolyte levels remained normal. There was a 20-lb. (9.1-kg.) weight loss. An obvious large, grapefruit-sized, smooth, tender, fixed mass was palpable in the middle of the upper part of the abdomen. At this juncture the patient became adept at removing and replacing his plastic nasogastric tube, leaving it out until vomiting became imminent or pain became too intense.

By the 28th hospital day operation seemed mandatory because of the nearly complete high intestinal obstruction and persistent pain. Gastric suction and parenteral alimentation were never effectively discontinued. An oral cholecystogram showed no filling of the biliary system and an upper gastrointestinal series (fig. 1) showed marked obstruction to flow of barium and the large mass displacing the stomach and duodenal loop anteriorly and superiorly.

On the 29th hospital day surgery was performed. A midline incision was made from xiphoid to umbilicus. Peripancreatic fat was hemorrhagic and edematous. The stomach was flattened and fixed anteriorly over a tense cystic mass occupying the whole lesser sac. The stomach was opened anteriorly and a trochar was inserted through the posterior wall into the mass; 1,650 cc. of pale green turbid fluid was removed. The amylase content was 486 units. The trochar opening was enlarged and the

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Chief, Medical Service, 3902d USAF Hospital, and Clinical Assistant, Department of Internal Medicine, University of Nebraska School of Medicine (Captain Nelp), and Chief, Surgical Service, 3902d USAF Hospital, and Instructor in Surgery, University of Nebraska School of Medicine (Lieutenant Colonel Marshall). Captain Nelp is now assistant resident on the Osler Medical Service, Johns Hopkins Hospital, Baltimore 5, Md. Lieutenant Colonel Marshall is now at Mitchell Air Force Base, New York.

area of the pancreas was explored digitally. The gland was nodular and friable. Fat necrosis was present. The cyst wall was remarkably thick and a 2-cm. cystogastrostomy was performed with continuous 0.0 chromic catgut. The gallbladder was tense, but no stones were felt. Further exploration or surgery was deemed inadvisable.

Postoperatively, the patient did well. At the end of a week he was taking small bland feedings. There was occasional mild postprandial epigastric distress. A second gastrointestinal series performed on the 13th postoperative day was essentially normal. No communication between cyst and stomach could be demonstrated.

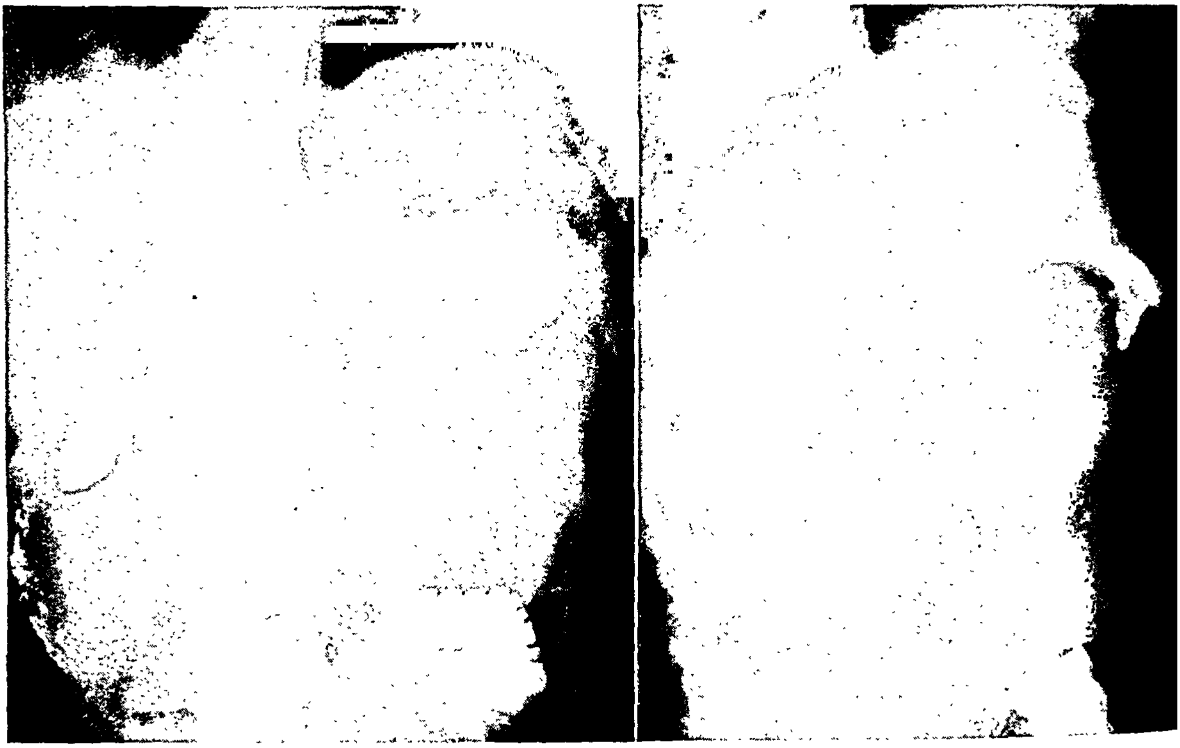

Fig. 1.—Gastrointestinal x-rays made on 28th day of illness, demonstrating large pseudocyst of pancreas. Barium w stilled with use of Levine tube.

A second cholecystogram showed filling of the gallbladder and multiple radiolucent stones. Two months after operation, the patient had regained his normal weight but had occasional postprandial burning. The serum amylase level had returned to normal and remained so.

The next week another operation was performed. The stomach appeared normal but was firmly affixed to the pancreas, obliterating the lesser sac. No evidence of pseudocyst was found. The cystic duct was thickened and dilated. The common duct appeared normal. Ten cubic centimeters of 35% iodopyracet (Diodrast) compound were injected by force of gravity into the isolated cystic duct segment. Retrograde filling of the pancreatic duct was seen (fig. 2). The common duct was explored and found free of stones. No larger than a no. 4 Ba
dilator could be made to pass through the sphin
of the ampulla. A transduodenal sphincteroto
was then performed, and afterward a no. 8 B
dilator could pass freely. Subsequent to sphincte
tomy the pancreatic duct was seen to enter the
tal third of the ampulla and was freely probed w
out obstruction. Cholecystectomy was then c
pleted and multiple small mixed bilirubin
cholesterol stones were found within the gallb
der. T-tube drainage was used. The patient's p
operative course was uneventful. Transient eleva
of the serum amylase level to 222 units was no
A cholangiogram made on the 12th postoper
day was normal and showed no evidence of
into the pancreatic duct (fig. 3).

The patient was last seen one year after
formance of the initial cystogastrostomy. He
maintained normal bowel function, he tolerate
foods well, and his physical findings were no

Comment

This patient presented several interesting
challenging features. The rapid development
pseudocyst was unsuspected, but its presence
be detected with some certainty 10 days
initial hospitalization. Its progressive enlarge
to the point of producing almost complete g
obstruction by the third hospital week made
gical intervention mandatory. Transgastric d

ge proved to be a relatively rapid, safe, and simple ethod in this case, in which the time and extent surgery needed to be minimized because of the tient's poor condition. His rapid recovery was deed gratifying; the gastrointestinal x-ray exami- tion on the 13th day postoperatively demonstrat- g no further evidence of the cyst and served to nphasize the effectiveness of this procedure. This nding was further verified at the subsequent opera- n two months after the initial procedure.

In 1923 Jedlicka successfully anastomosed a pan- eatic cyst remnant to the stomach after partial cision of a cyst, and Jurasz, in 1931, is credited ith the first transgastric cystogastrostomy.[1] The ocedure has since proved satisfactory in numer- s patients.[2] It has the obvious advantage of avoid- g an external drainage site, with the potential rbidity of chronic fistula formation and local in changes.

In a recent review Waugh and Lynn[2c] reported e course of 23 patients with pseudocyst treated by nple drainage and of 17 by marsupialization. ere was a mean drainage time of six and seven onths, respectively, in these two groups.

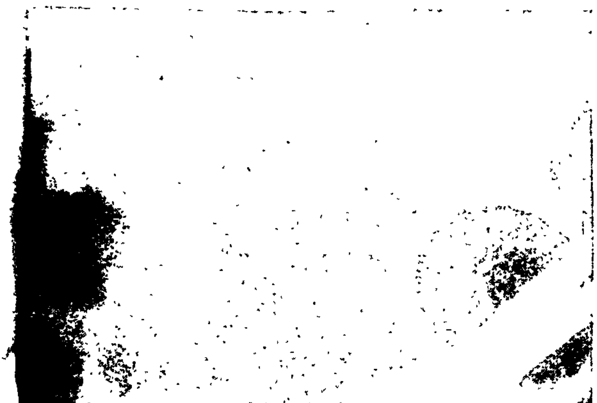

Fig. 2.—Operative cholangiogram made prior to sphinc- erotomy. Arrows point to reflux into pancreatic duct.

If drainage is adequate the granulation tissue ining of the cyst rapidly collapses and obliterates tself. Moreover, the stomach readily adapts in a hysiological manner to accepting pancreatic secre- ions directly—one need think only of the patient who takes his pancreatic secretion orally on a daily basis when plagued by a chronic draining external fistula.

Other surgeons[3] have been more restrictive in the use of internal drainage procedures for pancreatic cysts. The fear of overlooking a neoplastic lesion which may be curable by operation is a compelling reason for limiting such procedures. In such situations biopsy examination, with frozen section, would serve to clarify any question about the nature of the lesion. Recurrent cyst formation after cystojejunostomy or cystogastrostomy has also been cited as a significant deterrent. This, however, applies to all methods of pseudocyst drainage and only serves to emphasize that internal drainage alone is not a truly definitive procedure.

Fig. 3.—T-tube cholangiogram made on 12th day after performance of sphincterotomy, showing no pancreatic duct reflux—normal cholangiogram.

The omission of proper consideration of the biliary and sphincter components or other sites of obstruction in the pancreatic duct has been one of the major objections to pancreatic pseudocyst surgery consisting solely of internal drainage. In the present case, further definitive surgery was easily performed at the second operation. The patient did have cholelithiasis with small stones, an anatomically patent common biliary and pancreatic channel, and moderate stenosis of the sphincter of Oddi. Undoubtedly, the passage of one of the small calculi initiated his entire illness. The necessity for definitive correction of biliary and sphincter components in pancreatic cyst surgery has been strongly emphasized by Doubilet and Mulholland.[4] In less seriously ill patients internal drainage by cystogastrostomy and sphincterotomy with or without cholecystectomy could easily be combined.

Summary

A pancreatic pseudocyst developed rapidly and produced high intestinal obstruction after an initial attack of acute pancreatitis in a 21-year-old man who had cholelithiasis. Early internal drainage through cystogastrostomy followed in two months by cholecystectomy, choledochostomy, and sphincterotomy proved to be highly effective therapy. One year later, follow-up examination revealed apparently complete recovery.

602 N. Bond St., Baltimore 5, Md. (Captain Nelp).

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NEW SUCTION-LAVAGE SIGMOIDOSCOPE

Isio F. Wasserman, M.D., Utica, N. Y.

The greatest obstacle to a successful sigmoidoscopy is the presence of intestinal contents which delay or interfere with the examination or surgical treatment. The problem of incomplete evacuation has been obviated by repeated enemas, liquid diet, evacuant suppositories, and the introduction of sodium phosphate solutions having detergent effect. However, none of these methods provides a guarantee to the physician that the examination will not be delayed because of improper preparation.

Proper biopsy, the most reliable procedure for the identification of malignancy, requires generous samples taken from different questionable areas. Bleeding of varying degrees may follow the first attempt, interfering with the taking of further samples. Electrofulguration of bleeding points, often imperative, becomes a hazardous procedure if the areas are not well visualized.

Massive bleeding from the upper gastrointestinal tract, regardless of preparation or method of counteracting this complication, is a major threat to complete examination. Until the present, these problems have been met by the insertion of a suction tube or swab in the lumen of the sigmoidoscope in order to cleanse the area. The examiner's visibility is impaired while these instruments are in use and often they provide only temporary relief, since, when they are removed, blood will again cover the area in question.

The sigmoidoscope with a suction tube attached laterally to its wall is usually inadequate because the tube is of small diameter and suction is effective only at the point of contact of the tube with the inner lumen of the intestine.

New Model Sigmoidoscope

To overcome these difficulties, a new model sigmoidoscope is proposed. Essentially it consists of two tubes, telescoped within each other, which form a double wall with an inner chamber between them. This chamber is open at the insertion end and closed at the proximal end, at which an extension neck with a stopcock enables the inner chamber to be connected to a suction or injection apparatus. The injection process introduces cleansing agents into the intestine and, alternately, the ejection process suctions off excess fluid and gas.

The proximal end of the sigmoidoscope contains a lateral type of illumination. Although distal lighting gives excellent illumination with no shadows, frequent soiling of the lamp by feces or blood and the inconvenience of cleaning the smeared bulb

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Attending Surgeon, St. Luke's-Memorial Hospital Center, New Hartford; Attending Surgeon, St. Elizabeth's Hospital; and Attending Proctologist, Oneida County Tumor Clinic.

offset this advantage. With proximal lighting, visibility is diminished because the light source is set in the ocular system. Therefore, the lateral type of illumination, previously used by Yeomans,[1] has been improved on by use of a larger bulb, with increased wattage; burned-out bulbs can easily be removed and replaced since they are of the standard, screw-in type, costing about 15 cents apiece at any electrical supply store.

Method of Operation.—The instrument is introduced with the usual technique. When suction is indicated, the rubber tube of the suction machine is connected to the stopcock extension, enabling the chamber system to act as a constant or intermittent suction conductor at the distal end of the instrument. Any liquid in the intestinal lumen is channeled through the inner chamber and out to the container of the suction machine. Suction at the distal end is applied concentrically, thus keeping the area under observation clear of intestinal content (fig. 1). This is to be compared with the standard method of lateral suction tube drainage, in which only a small area is drained because of the limited size and suction power of the tube.

If examination is impeded by the patient's incomplete evacuation, an injection machine is attached to the stopcock of the sigmoidoscope; saline solution or sodium phosphate is introduced into the intestine and consequently withdrawn (by reversing the action to suction) to a separate container. This operation will effect a thorough washing and cleansing of the intestine. If an injector machine is not available, the detergent agent may be flushed directly through the inner lumen of the sigmoidoscope, to be retrieved by suction.

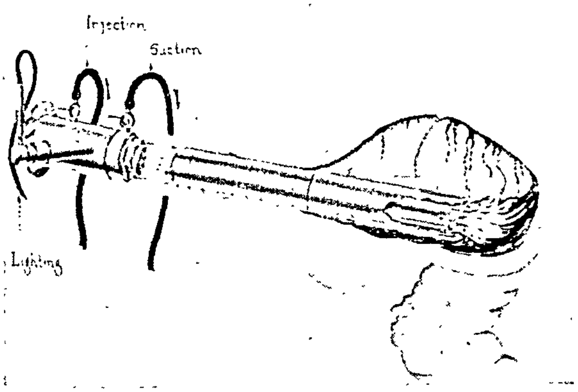

Fig. 1.—Continuous suction of intestinal content, achieving clear field.

Comment

If the patient is not properly prepared for examination, valuable time is lost for both physician and patient. The patient must be subjected to the undue stress of another sigmoidoscopy and the suction or swabbing has yet to be applied in order to remove intestinal contents. With this instrument, even if further cleansing is necessary, the sigmoidoscope need not necessarily be displaced, and the intestinal contents can be removed under direct visual control. The procedure of cleansing and suction can be repeated as many times as is required to be effective, and the examination can then continue. The same principle can be applied for diagnosis in a patient with massive bleeding. The bleeding of varying degrees which follows a first attempt at taking a biopsy specimen can easily be controlled, since the suction, concentrically applied, maintains a clear, dry area. Further samples can be taken under direct and constant visualization.

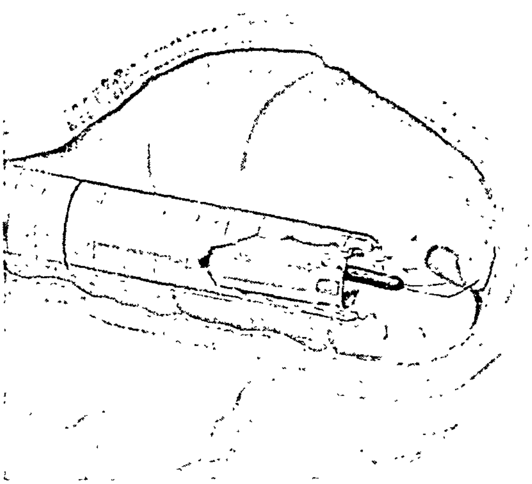

Fig. 2.—Prevention of explosion during fulguration by continuous suction of flammable gas. When necessary, inert gas is injected through suction chamber.

Surgical diathermy in the intestinal lumen, for the removal of polyps, hemostasis, or palliative treatment of carcinoma, is a surgical procedure which is extensively used. Arnous,[1A] Moutier,[2] Carter,[3] and Becker[4] reported cases of intestinal rupture due to gas explosion. Many such cases of explosion remain unreported, because of either lack of subsequent complications or poor understanding of the problem and the dangers involved. Explosion is caused by the effect of sparking on the high concentration of methane and oxygen in the intestine. Arnous[1] and Becker[4] suggested the use of a free tube which could carry carbon dioxide to the site while electrosurgery was performed, thus isolating the area by an atmosphere of inert gas. Another tube, either free-standing or attached to a sigmoidoscope, must be used to remove the resultant smoke. Obviously, the disadvantage of using an extra instrument in the inner lumen of the sigmoidoscope is the obstruction to visibility.

In my opinion, explosions will be prevented if there is sufficient suction to assure the complete expulsion of all potentially flammable gases. Carbon dioxide, when preferred, can be injected through the suction chamber and visibility is unimpaired (fig. 2).

Finally, it must be emphasized that, since suction in the proposed sigmoidoscope is applied in a constant manner, there is no need for superfluous instruments to be added. While the vision is kept free of any obstacle, the hands of the operator are available for further procedures.

264 Genesee St.

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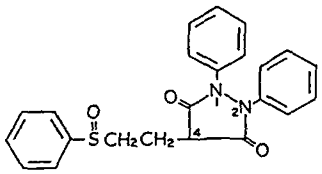
COUNCIL ON DRUGS

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. Kautz, M.D., *Secretary.*

Sulfinpyrazone (Anturan).—1,2-Diphenyl-4-(2′-phenylsulfinethyl)-3,5-pyrazolidinedione.—The structural formula of sulfinpyrazone may be represented as follows:



Actions and Uses.—Sulfinpyrazone, a pyrazolone derivative chemically related to phenylbutazone, is a potent uricosuric agent employed in the management of gout. It is useful primarily in the prevention, rather than the treatment, of attacks of acute gouty arthritis. The severity and frequency of such attacks are reduced by continuous long-term administration of the drug, presumably by virtue of its ability to promote the renal excretion of uric acid. The maximal increase in uric acid excretion obtainable with sulfinpyrazone is comparable to that with probenecid, whereas the dose required for equivalent effects is smaller. Nevertheless, although most patients experience some reduction in the serum uric acid concentration, normal values cannot be achieved in all patients. Patients refractory to other uricosuric agents may respond to sulfinpyrazone.

In chronic gout, sulfinpyrazone suppresses formation of new tophi and may reduce the size of old tophaceous deposits and alleviate joint pain and stiffness. However, improvement usually becomes apparent only after several weeks or months of treatment. Most patients require the concomitant use of colchicine or of other drugs for adequate symptomatic relief, since sulfinpyrazone has only weak, if any, analgesic or anti-inflammatory action. For similar reasons, colchicine, phenylbutazone, and other analgesics are not replaced for the relief of pain and the other manifestations of acute gout.

Sulfinpyrazone is rapidly and completely absorbed from the gastrointestinal tract; about one-half of a single dose is excreted or metabolized within three hours. Experimental studies reveal that sulfinpyrazone increases the renal clearance of uric acid, depresses clearance of para-aminohippuric acid, and has little effect on the clearance of inulin. These observations suggest that, like probenecid, it produces its uricosuric effect by preventing tubular reabsorption of uric acid, without altering the rate of glomerular filtration.

Salicylates, which even in small doses strongly antagonize its uricosuric action, should not be administered with sulfinpyrazone. There is no known contraindication to the conjunctive use of phenylbutazone, probenecid, or zoxazolamine with sulfinpyrazone, however.

Side-Effects.—An acute attack of gouty arthritis is sometimes precipitated shortly after treatment with sulfinpyrazone is begun, and the frequency of acute attacks may be increased for several weeks thereafter. For this reason, the prophylactic administration of colchicine during the first few weeks of treatment has been recommended.

The marked increase in urate excretion induced by sulfinpyrazone sometimes provokes urolithiasis and renal colic. In order to minimize the incidence of this complication, eradication of preexisting urinary tract infections and administration of sufficient fluid and alkali to insure a large volume of alkaline urine are indicated. The drug should be used only with great caution, if at all, in patients with impaired renal function; in such cases, periodic tests of renal function should be performed.

Epigastric distress and other gastrointestinal symptoms are among the most frequent complications of treatment with sulfinpyrazone; activation of quiescent peptic ulcer has been reported. Hence, it is suggested that sulfinpyrazone be administered with food, milk, or alkali. The drug is contraindicated in patients who have, or who have recently had, an active peptic ulcer.

Leukopenia and thrombocytopenia have each been reported in a single patient taking the drug. In neither instance, however, was the effect definitely ascribable to the drug. Nevertheless, because of the known propensity of a number of other pyrazolone derivatives to depress hematopoietic function, all patients receiving sulfinpyrazone should have blood cell counts done at regular intervals. Experience with this agent has been relatively limited, and it is not yet possible to estimate the hazard of more serious toxic effects, such as those of the parent compound phenylbutazone, when sulfinpyrazone is given over protracted periods.

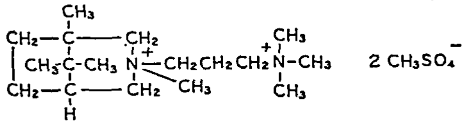
Dosage.—Sulfinpyrazone is administered orally, preferably with meals or with milk. The dose is 50 mg. four times daily, initially, and is gradually increased over a period of a week, until a total daily dosage of 400 to 800 mg. is reached. After a satisfactory reduction of the blood urate level has been achieved, somewhat lower doses, adjusted in accordance with the requirements of the individual patient, are often sufficient for maintenance. Treatment should be continued without interruption. Acute exacerbations of gout do not necessitate discontinuance, but, as previously mentioned, may require the concomitant use of colchicine, phenylbutazone, or other drugs.

Preparations.—tablets 100 mg.

Year of introduction: 1959.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, cooperated by furnishing scientific data to aid in the evaluation of sulfinpyrazone.

Trimethidinium Methosulfate (Ostensin).—*d*-[N-Methyl-N-(γ-trimethylammoniumpropyl)]-1-methyl-8,8-dimethyl-3-azabicyclo[3.2.1]octane dimethosulfate.—The structural formula of trimethidinium methosulfate may be represented as follows:



Actions and Uses.—Trimethidinium methosulfate, a quaternary ammonium compound, is used in the treatment of hypertension. The principal pharmacological effects of the drug are referable to autonomic ganglionic blockade. In addition, trimethidinium also exerts some degree of centrally mediated activity. In terms of weight of drug required to produce comparable reductions in blood pressure, trimethidinium is more potent than hexamethonium but less so than mecamylamine. Its duration of action lasts about 7 to 12 hours after oral administration. The absorption of orally administered trimethidinium methosulfate is not complete, but it is reasonably regular and predictable when given to patients in a fasting or near-fasting state.

The clinical use of trimethidinium should be restricted to those patients with moderate to severe forms of diastolic hypertension who fail to respond adequately to therapy less drastic than ganglionic blockade. Ganglionic blocking agents should not be given for mild, labile hypertension. When indicated, orally administered trimethidinium will usually lower both systolic and diastolic blood pressure. The adjunctive use of chlorothiazide or reserpine may afford additional symptomatic relief and allow for reduction in the daily dose of trimethidinium. Tolerance to trimethidinium may occasionally develop after a stage of initial sensitivity; in such cases, however, if therapy is continued and the dose gradually increased, usually an antihypertensive effect can again be produced. Secondary tolerance has not been reported.

Therapy with trimethidinium should be undertaken cautiously, with the realization that the drug is capable of producing the full spectrum of pharmacological side-effects referable to ganglionic blockade. These include blurring of vision, postural hypotension, dryness of the mouth, constipation, interference with sex functions, weakness, nervousness, malaise, dizziness, and headache. Present evidence indicates that trimethidinium causes visual disturbances more often than do mecamylamine or hexamethonium. It shows a lower incidence and severity of certain other side-effects, such as constipation and paralytic ileus, common to other ganglionic blocking agents. The drug should be administered cautiously, if at all, in the presence of marked renal insufficiency, especially when there is elevation of blood nonprotein nitrogen levels. Patients with coronary insufficiency, recent myocardial infarction, cerebral thrombosis, and severe, generalized atherosclerosis should not be treated by ganglionic blockade. Other contraindications to the drug include glaucoma, organic pyloric stenosis, bleeding peptic ulcer, and uremia.

Dosage.—Trimethidininum methosulfate is administered orally. Dosage must be highly individualized according to the response of the particular patient and the appearance and severity of side-effects.

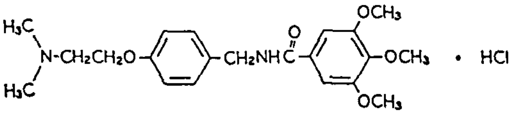
Oral therapy is initiated by the administration of 20 mg. before breakfast and again before the evening meal. Dosage is then increased by increments of 20 mg. every third day until a satisfactory response is obtained. The ultimate total daily dose may vary from 20 to 480 mg.

Preparations.—tablets 20 mg. and 40 mg.

Year of introduction: 1959.

Wyeth Laboratories, Division of American Home Products Corporation, cooperated by furnishing scientific data to aid in the evaluation of trimethidinium methosulfate.

Trimethobenzamide Hydrochloride (Tigan Hydrochloride).—N-(Dimethylaminoethoxybenzyl)-3,4,5-trimethoxybenzamide hydrochloride.—The structural formula of trimethobenzamide hydrochloride may be represented as follows:



Actions and Uses.—Trimethobenzamide hydrochloride, proposed for use as an antiemetic agent, is reported to be helpful in alleviating nausea and reducing the frequency of vomiting in the immediate postoperative period; in pregnancy; in motion sickness; in intoxication from digitalis, nitrogen mustard, and other drugs; and in such pathological conditions as malignancy, hepatitis, cholecystitis, uremia, alcoholic gastritis, labyrinthine disease, and radiation sickness. Although the early clinical reports are favorable, many are based on uncontrolled trials in which no comparisons with placebos or with other similar drugs were made, and the results obtained are difficult to appraise accurately. Nevertheless, the few comparative studies thus far reported suggest that trimethobenzamide hydrochloride has significant antiemetic activity. Effects appear within 20 to 40 minutes after either oral or intramuscular administration and persist for three to four hours.

Side-Effects.—No evidence of serious toxicity has accompanied the use of trimethobenzamide hydrochloride; adverse effects on the liver, kidney, or bone marrow have not been noted. However, most studies have been short-term trials, and further studies are greatly needed to establish definitely the safety of the drug for long-term use. Although the incidence of minor side-effects is not high, drowsiness, vertigo, diarrhea, exaggeration of preexisting nausea, pain at the site of injection, and local irritation after rectal administration have been reported. Administration prior to or during anesthesia apparently does not prolong awakening time. A sudden fall in blood pressure has been observed in one patient shortly after an injection of trimethobenzamide hydrochloride given during the postoperative period; however, it is questionable whether this complication was due to the action of the drug.

Experimental Pharmacology.—In animals, trimethobenzamide hydrochloride effectively inhibits apomorphine-induced vomiting, and is thus presumed to act primarily by depressing the chemoreceptor trigger zone; the possibility that depression of the medullary vomiting center may also contribute to its antiemetic effect has not been excluded, however. The antiemetic potency of trimethobenzamide hydrochloride is about one-tenth that of chlorpromazine when given subcutaneously and one-fourth that of the latter when given orally. When equieffective antiemetic doses of the two agents are compared, trimethobenzamide hydrochloride is the less active depressant of the central nervous system, as measured by degree of sedation, modification of behavior, prolongation of barbiturate sleeping time, and changes in the electroencephalogram.

Although trimethobenzamide resembles diphenhydramine and several other histamine-antagonizing agents in being an ether of dimethylaminoethanol, it seems to have only weak antihistaminic activity. Nor does it appear to antagonize the effects of epinephrine or of acetylcholine. An intravenous injection, in animals, produces a fall in blood pressure and an increase in bronchial tone.

Dosage.—Trimethobenzamide hydrochloride is administered orally, rectally, or intramuscularly. In adults, the recommended dose is 100 to 300 mg given orally or intramuscularly four times daily However, the effects of the larger doses within this range, when administered over prolonged periods have not been thoroughly explored. When given rectally, the dose is 200 mg. For the prevention o postoperative vomiting, a single dose of 200 mg. i given intramuscularly prior to or during surgery this dose may be repeated three hours after th termination of anesthesia, if necessary.

In children, the aforementioned doses are reduced, in proportion to their body weight. For th prevention of postanesthetic vomiting, the following single doses are given intramuscularly: in children weighing less than 30 lb. (13.6 kg.), 50 mg in those weighing 30 to 60 lb. (27.2 kg.), 100 mg 60 to 90 lb. (40.9 kg.), 150 mg.; and over 90 lb 200 mg.

Preparations.—capsules 100 mg.; solution (injection) 200 mg. in 2 cc.; suppositories 200 mg.

Year of introduction: 1959.

Roche Laboratories, Division of Hoffmann-LaRoche, Inc cooperated by furnishing scientific data to aid in the evaluation of trimethobenzamide hydrochloride.

Parenteral Use of Triamcinolone Acetonide (Kenalog)

Triamcinolone acetonide is a highly potent, synthetic gluco-corticoid, which was described previously for topical use in the treatment of certai acute or chronic dermatoses (*J. A. M. A.* 170:19 [May 9] 1959). The Council subsequently ha evaluated its usefulness and safety for parentera (intra-articular, intrasynovial, intrabursal) injectio in the treatment of painful and inflammatory cond tions of the joints, bursae, and tendon sheath When injected at these sites, the drug is usuall effective in relieving the joint pain, swelling, and stiffness associated with rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, synovitis, and other conditions amenable to the anti-inflammatory action of locally injected gluco-corticoids. In responsive persons, beneficial effects generally appear within a few hours after injection and persist for periods of one to several weeks.

Systemic steroidal effects due to injection of triamcinolone acetonide are rare, if care is taken to guard against infiltration of the drug into soft tissues surrounding the joint. Painful local reactions at the site of injection have been reported only occasionally. Infrequently, dizziness and transient flushing may be encountered. Intra-articularly injected triamcinolone acetonide is contraindicated in patients with gonococcal or tuberculous arthritis or other infections in or near the joints.

The techniques of intra-articular injection of triamcinolone acetonide are the same as those ordinarily employed for other agents used by this route. If desired, a local anesthetic may be infiltrated into the surrounding soft tissues prior to the intra-articular injection. An aqueous suspension containing 10 mg. in 1 cc. is used. Dosage is variable and depends on the size of the joint and severity of symptoms. For small joints, amounts containing 2.5 to 5 mg. are generally used; for larger joints, the dose may range from 5 to 15 mg. Frequency of administration is determined by the duration of response.

The Council voted to amend the monograph on triamcinolone acetonide to describe its parenteral use.

E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, cooperated by furnishing scientific data to aid in the evaluation of the parenteral use of triamcinolone acetonide.

CLINICAL SCIENCE

NEWER APPROACHES TO ANTIHYPERTENSIVE THERAPY

Albert N. Brest, M.D.
and
John H. Moyer, M.D., Philadelphia

During the past decade a large number and variety of potent antihypertensive agents has been developed. These include Veratrum alkaloids, Rauwolfia compounds, hydralazine, ganglioplegic agents, and adrenergic-blocking drugs. The therapeutic actions of these compounds are directed primarily at the central mechanisms of sympathetic impulse formation or the peripheral sites of neurogenic transmission, or both (fig. 1). The more recent antihypertensive medicaments which are being developed, however, have much different mechanisms of action. It is the purpose of this report to discuss specifically those newer compounds which (1) affect catecholamine release, (2) alter fluid and electrolyte balance, and (3) interfere with enzymatic activity.

Antihypertensive Agents Which Affect Cathecholamine Release

Norepinephrine and epinephrine are catecholamines which are normally released by the postganglionic sympathetic fibers in response to sympathetic impulse transmission. These catecholamines, in turn, stimulate the peripheral neuroeffector site, thereby producing arteriolar vasoconstriction and a secondary increase in the arterial blood pressure.

The most important group of currently available antihypertensive drugs which affect catecholamine release is that of the Rauwolfia compounds. The earlier investigations into the mechanism of action of these compounds indicated that serotonin is released from binding sites within the brain. More recently it has been determined that Rauwolfia also releases catecholamines centrally from the hypothalamic centers, and in addition it has been found that catecholamines are released peripherally from the postganglionic sympathetic nerve fibers as well.[1] The latter effect depletes the sympathetic fiber of its catecholamine stores and thereby decreases the response to various pressor stimuli. These studies provide a better insight into the basic pharmacodynamic actions of this important group of antihypertensive agents.

Syrosingopine is a chemical modification of reserpine which exhibits predominantly hypotensive action with lesser central sedative effects. It appears that the hypotensive action of the latter compound is related primarily to its ability to release catecholamines from peripheral structures, whereas its reduced central effects are apparently due to a lesser capacity to liberate these amines from their central stores.[1] This type of pharmacological modification will undoubtedly continue and may eventually result in the development of even more potent hypotensive compounds.

Director, Hypertension Unit (Dr. Brest), and Professor of Medicine (Dr. Moyer), Hahnemann Medical College.

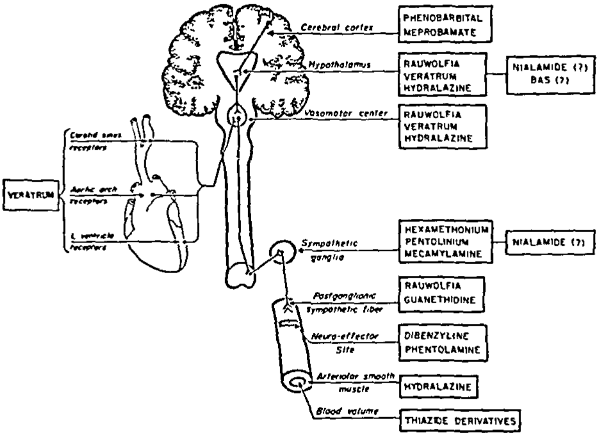


Fig. 1.—Diagrammatic illustration of various antihypertensive agents and their pharmacodynamic sites of action.

There is presently being developed a group of antihypertensive compounds, including guanethidine, whose mechanism of action appears to be an inhibition of the peripheral release of catecholamines from the postganglionic sympathetic nerve fibers. The activity of the sympathetic nervous system and the subsequent release of catecholamines is normally increased when the upright position is assumed. Guanethidine inhibits the usual response to this righting reflex, and blood pressure reduction thereby ensues. Preliminary studies by Page and Dustan[2] have suggested the marked hypotensive abilities of this compound, and subsequent studies[3] tend to confirm the effectiveness of this drug (fig. 2).

The blood pressure reduction obtained with guanethidine is predominantly a postural one and is therefore similar to that obtained with the ganglionic blocking compounds. However, in contrast to the ganglioplegic drugs, guanethidine produces a significant hypotensive response without the associated side-effects due to parasympathetic blockade. Side-effects encountered to date have indeed been minimal, with mild diarrhea as the only significant complaint even when large daily doses (450 mg.) of the drug are administered. No evidence of toxic action of the drug has been encountered thus far.

The dose of guanethidine needed to maintain a satisfactory hypotensive response has ranged from 25 to 450 mg. per day (average dose, 100 to 150 mg. daily). As with all of the other available antihypertensive agents, the concomitant administration of a thiazide derivative potentiates the blood pressure reduction obtained, thereby enhancing the therapeutic efficiency of the newer compound.

The blood pressure response to a single test dose of guanethidine given by mouth does not appear to be a reliable guide to the subsequent response. In fact, a significant blood pressure reduction may not be noted for 24 to 48 hours after the initiation of therapy. It is therefore recommended that at least 48 to 72 hours elapse before the daily dosage is increased. Also, since blood pressures fall more markedly in a patient who is standing than in one who is lying down, it would appear logical for the patient to sleep with the head of the bed elevated on 10-in. to 12-in. blocks in order to obtain the maximum therapeutic benefit from this drug.

The development of potent antihypertensive agents whose major effect is directed at peripheral catecholamine release promises to be an important contribution to the therapeutic armamentarium for diastolic hypertension.

Antihypertensive Agents Which Alter Fluid and Electrolyte Balance

The most important group of antihypertensive agents which has become available during recent years is that of the thiazide derivatives. The introduction of chlorothiazide as a hypotensive agent was followed by almost immediate clinical acceptance because of its potent antihypertensive qualities, its ability to potentiate the effectiveness of other hypotensive compounds, and the low incidence of associated side-effects and untoward reactions. Subsequently, several newer members of the benzothiadiazine family, including hydrochlorothiazide, flumethiazide, and hydroflumethiazide, have become available for clinical use.

A recent study[4] indicated that chlorothiazide, hydrochlorothiazide, and flumethiazide produce similar hypotensive responses when used in comparable (diuretic and natruretic) dosages. A significant hypotensive effect was obtained in about 40% of 121 hypertensive subjects, when they were in the supine position, and a slightly greater postural hypotensive response was induced (see table). The incidence of side-effects encountered was small with each of the drugs and, similarly, the incidence of beneficial effects obtained did not indicate an outstanding advantage for any one of the three compounds.

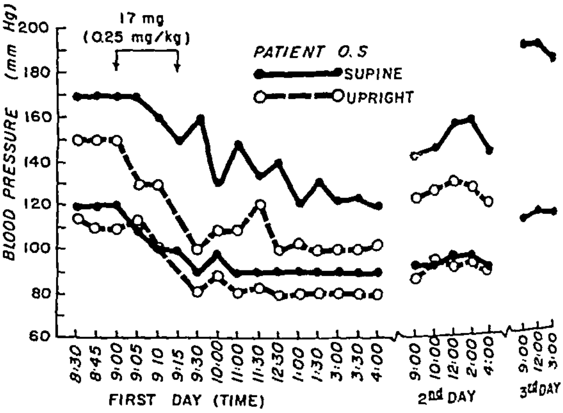


Fig. 2.—Blood pressure response to intravenously given guanethidine. Significant hypotensive response was obtained with single parenteral infusion of guanethidine, and blood pressure reduction was sustained for 48 hours.

The antihypertensive effect achieved with the thiazide derivatives is, of course, by no means unique. A similar hypotensive response can be obtained with the use of a rigid low-salt diet or the parenteral administration of mercurial diuretics. Unfortunately, in order to achieve a significant blood pressure reduction, the patient's dietary intake of salt must be reduced to 500 mg. per day or less, and there are few patients who will adhere to such a rigid dietary regimen for any significant period of time. Likewise the administration of daily injections of mercurial diuretics is obviously unsatisfactory from a practical standpoint. Thus the development of potent, well-tolerated diuretic substances which can be effectively administered orally must be considered a major contribution to the drug therapy of essential hypertension.

The antihypertensive mechanism of the thiazide derivatives is as yet undetermined. The initial pharmacodynamic studies[5] suggested that their hypotensive effect was related to a *reduction in plasma volume*, which resulted from the diuresis of sodium and chloride ions and the accompanying loss of water stores from the extracellular space. The subsequent decline in the cardiac output could thereby account for the ultimate reduction in the arterial blood pressure. However with the continued use of these drugs there is a reaccumulation of plasma volume[6] which is probably due to the migration of fluid from the extracellular space into the intravascular compartment. Thus, the original postulate appears to be an unlikely explanation.

Blood Pressure Response to Three Thiazide Derivatives

Drug*	Patients, No.	Supine, %			Upright, %		
		Normotensive†	Mean Blood Pressure Reduced >20 mm. Hg or Normotensive	Unresponsive	Normotensive†	Mean Blood Pressure reduced >20 mm. Hg or Normotensive	Unresponsive
Chlorothiazide	50	18	36	64	24	46	54
Hydrochlorothiazide	54	20	39	61	22	39	61
Flumethiazide	17	12	41	59	47	53	47

* The dose of chlorothiazide was 500 mg. b.i.d., hydrochlorothiazide 50 mg. b.i.d., and flumethiazide 500 mg. b.i.d.
† Blood pressure reduced to 150/90 mm. Hg or less.

One important facet about which we know little concerns the local effects which are induced within the intracellular compartment due to changes in electrolyte patterns. These effects might conceivably be the most important of all, and Preziosi and co-workers[7] reported some interesting experimental observations which did indeed suggest a local depressant action on the peripheral vascular smooth muscle. Further confirmation of these findings must be awaited.

Regardless of the precise mechanism of action of these compounds, it would appear that their antihypertensive abilities are related to their diuretic and natruretic effectiveness. Thus, when comparable doses of the various thiazide derivatives are administered, *similar hypotensive responses* are obtained.

Antihypertensive Agents Which Interfere with *Enzymatic Activity*

There is currently being developed another group of antihypertensive compounds whose major effect is apparently related to an interference with enzymatic (specifically, monoamine oxidase) activity. Monoamine oxidase (MAO) is an enzyme which actively destroys various monoamines including norepinephrine, epinephrine, and serotonin. It would therefore be anticipated that the MAO inhibitors would cause an accumulation of these hormones in muscle and nerve tissues, where they normally account for smooth muscle contraction and neurogenic transmission. Hence it seems rather paradoxical that hypotension should occur, since the expected result would be a hypertensive response secondary to the increased concentration of these pressor substances. It is of interest in this regard that many patients with norepinephrine-producing tumors (pheochromocytomas) may have a *supine elevation of blood pressure but a marked postural hypotensive effect*; and, similarly, hypotensive episodes may also occur in patients with hyperserotonemia due to malignant carcinoid tumors.

Any statement concerning the mechanism by which the monoamine oxidase inhibitors lower blood pressure is entirely speculative at this time. Some insight into their hypotensive abilities, however, may be obtained from a review of their clinical actions. The hypotensive response is mainly a postural one and the side-effects which have been reported (with iproniazid and other MAO inhibitors)[8] are similar to those encountered with the ganglionic blocking agents. These have included blurring of vision, dryness of the mouth, constipation, and urinary difficulty. The combination of these two clinical findings has therefore suggested that their mechanism of action may be due primarily to ganglionic blockade.

Brodie[9] has postulated that norepinephrine and serotonin act as neurohormones within the central nervous system to control and regulate the various autonomic, somatic, and psychogenic functions. Since the use of the MAO inhibitors can be expected to result in an increased concentration of these substances within the brain tissue, it is conceivable that the hypotensive abilities of these compounds may be intimately involved with this particular effect. However, much more investigative work needs to be accomplished in this regard.

In summary, the clinical actions of the monoamine oxidase inhibitors suggest that these compounds might be ganglionic blocking agents as well as monoamine oxidase inhibitors. Whether these two actions are separate or interrelated is uncertain at this time. However, regardless of the precise mechanism of action, continued study of these compounds in patients with hypertension is warranted and may, indeed, ultimately provide a clue to the pathogenesis of this important disease process. Finally, because of the additional beneficial effects of the monoamine oxidase inhibitors in the therapy of angina pectoris, it may well be that these drugs will be particularly indicated in the hypertensive subject with complicating coronary artery disease.

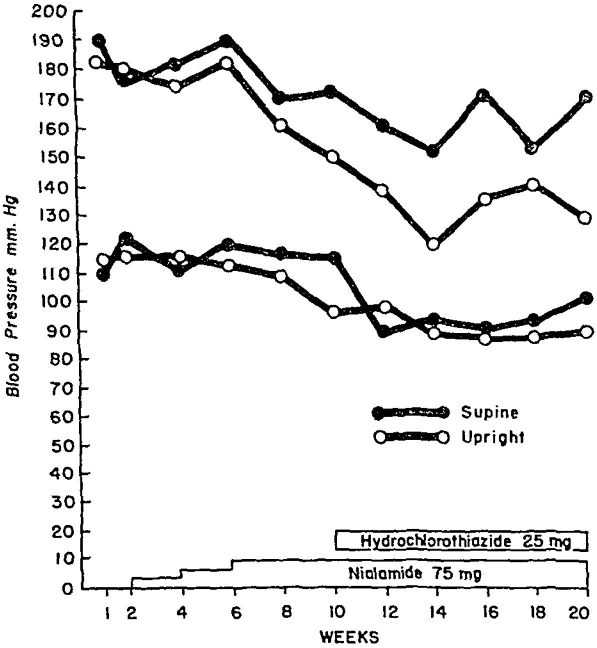


Fig. 3.—Response of patient to combined antihypertensive medication. Although significant postural hypotensive response was obtained with combination of nialamide (75 mg. t. i. d.) and hydrochlorothiazide (25 mg. b. i. d.), supine blood pressure remained elevated.

Our own experience[10] with the monoamine oxidase inhibitor nialamide, used alone and also in combination with hydrochlorothiazide, tends to confirm the clinical findings reported by other investigators; that is, although these compounds are indeed capable of effectively reducing blood pressure when used alone, they are considerably more effective when used in combination with the thiazide derivatives. It is also apparent that the hypotensive response which is obtained with these agents (whether used alone or in combination, or both) is most pronounced when the patient is in the upright position (fig. 3). The patient with moderate or severe hypertension should be started on therapy with hydrochlorothiazide, 50 mg. twice daily, and nialamide, 25 mg. three times daily. Thereafter the nialamide dosage can be doubled at 7-day to 14-day intervals, to a maximum of 100 mg. three times daily, unless an adequate response occurs at a lower dosage.

Summary

The therapeutic actions of most of the currently available antihypertensive agents are directed primarily at the central mechanisms for sympathetic impulse formation or at the peripheral sites of neurogenic transmission, or both. There are presently being developed a variety of newer compounds which affect other important pharmacodynamic sites. These include agents which affect the central or peripheral release of catecholamines, alter fluid and electrolyte balance, and interfere with enzymatic activity. The use of these newer agents provides a more diversified approach to the therapy of essential hypertension and possibly a better insight into the mechanisms involved.

230 N. Broad St. (2) (Dr. Moyer).

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SPECIAL CONTRIBUTION

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS POLICY FOR FOREIGN MEDICAL GRADUATES

"Regardless of the date of appointment, it is expected that all graduates of foreign medical schools serving as interns or residents in U. S. hospitals as of July 1, 1960, will have been certified by the Educational Council for Foreign Medical Graduates."

The above policy statement was sent to all hospitals conducting intern and resident programs and was published in The Journal of the American Medical Association, July 19, 1958. It does not apply to those foreign medical graduates who possess a full and unrestricted license to practice in the United States or its territories or possessions. Persons holding such licenses are advised, however, that ECFMG certification may be required when seeking reciprocity from other states.

The CMEAH was supported by the wholehearted reaffirmation of the July 1, 1960, cut-off date by the House of Delegates at its December, 1959, meeting. However, the House of Delegates directed that the above policy be implemented judiciously where local circumstances warrant. Accordingly, in implementing this policy, the following will pertain.

After July 1, 1960, no hospital should expect to maintain an approved internship or residency program unless its appointees who are graduates of foreign medical schools either (1) have a full and unrestricted state license to practice, (2) are in their final six months of training, (3) have secured a standard or temporary certificate from the ECFMG, or (4) have been given a contingent appointment for not more than six months based on their having been accepted for the September, 1960, American medical qualification examination of the ECFMG. Extension of the appointment beyond Dec. 31, 1960, will be dependent upon the appointee receiving temporary or standard certification from the ECFMG as a result of this examination.

It is a requirement of the law that institutions must notify the Immigration and Naturalization Service of changes in the appointments of those trainees who are in this country on temporary or student visas under the exchange-visitor program. This is not a requirement in the case of the permanent immigrant.

Each hospital making contingent appointments on or after July 1, 1960, should do the following:

a. Include in the contract or letter of agreement with the foreign medical graduate a statement that the appointment will be terminated on or before Dec. 31, 1960, and the Immigration and Naturalization Service notified if the candidate fails the September, 1960, AMQ examination. (It appears to the CMEAH that it is inappropriate to offer such an appointment to a foreign medical graduate who is not now in the U. S. In this event, it would seem morally indefensible to make such a contingent appointment with the result that the foreign graduate might spend only six months in this country.)

b. In all such instances of failure of the AMQ examination by a foreign medical graduate who is on the exchange-visitor program, address a letter promptly to the Immigration and Naturalization Service stating the date on which the individual's appointment will be terminated.

c. Forward a copy of the above letter to the CMEAH so the record of the hospital program can be cleared.

d. In the case of foreign medical graduates who have permanent immigrant or citizenship status, a similar letter should be addressed directly to this Council for action as stated in "c."

e. Check all other appointments to be certain that those noncertified foreign medical graduates are either in their final six months of training or have a license to practice in a state, territory, or possession of the United States.

Basis for Council on Medical Education and Hospitals Policy Implementing Certification by the Educational Council for Foreign Medical Graduates

"The Essentials of an Approved Internship and Essentials of Approved Residencies" state that "the development of a satisfactory program requires first of all, careful selection of applicants for appointment to the (intern or resident) staff. . . . The qualifications of the (intern or resident) staff should leave no doubt as to their competence to accept this assignment since the primary obligation of the hospital must be for the patients' welfare."

"The Essentials" further state: "The Council recommends that hospitals considering foreign medical school graduates for (internship or residency) positions acquire reasonable assurance in regard to their medical qualifications through utilization of the program of the Educational Council (or Foreign Medical Graduates)."

After July 1, 1960, the CMEAH will recommend to each review committee the disapproval of those training programs whose rosters contain graduates of foreign medical schools who do not satisfy requirements 1, 2, 3, or 4.

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OPERATING ROOM INFECTION

IN THE latter half of the 19th century, Lord Joseph Lister,[1] on the basis of Pasteur's work and his own investigations, introduced, as part of his aseptic technique, the carbolic spray, in an attempt to free the air of the operative field of pathogenic bacteria. It was soon demonstrated, however, that contact contamination overshadowed any other source of inoculation of an open wound. As a result, aseptic technique was developed, with the principal objective of sterilizing, or, if unable to sterilize, of cleansing thoroughly everything except the air that came in contact with the wound. Contact inoculations have thus been controlled relatively satisfactorily. Masking, first of the mouth and later of the mouth and nose, by a technique inadequate at best, has long been advocated and widely adopted to prevent droplet contamination. The importance of "droplet nuclei" of bacteria, which will pass through most masks and lead to contamination of the air, is more generally recognized but has not been controlled. Bacteria in the air may float for varying periods of time and settle on the exposed "sterile field" and wound.

In the early days of "aseptic surgery" it was recognized that, despite the adoption of rigid precautions, some bacteria were present in every surgical wound, and a technique designed to leave the wound in the best condition for the body defenses to overcome this "irreducible minimum" of bacteria was developed. "Unexplained" infections were reduced and only occasionally were fatal. The "golden age of surgery" was ushered in, with more and more areas of the body becoming accessible to operations of greater and greater magnitude, duration, and trauma. No area of the body is inaccessible today to the trained surgeon. However, with these larger, more traumatizing, and longer procedures, "unexplained infections" have become progressively more common and more critical. In years past, infections associated with epidemics of respiratory tract contamination, particularly streptococcic, were critical in some instances. Postoperative infections after the widespread dissemination of hemolytic streptococci during and after the influenza epidemic of 1918-1919 became so frequent and so serious that some hospitals closed their operating rooms except to emergency cases. Staphylococci have now taken a front line stand and form a major group of respiratory tract contaminants. Dissemination of these pathogens may reach epidemic proportions during the colder months.

Despite this information and the studies that have related peaks of wound infections with epidemics of respiratory tract disease, the air as a route of spread of bacteria has been overlooked by some surgeons, except for "token masking" and restrictions at times on talking in the operating room. In contrast, attempts to control contact contamination have been continuous and have resulted in an ever-improving sterile technique which has been extended occasionally to produce such innovations as the "no-touch technique" for bone grafts. It should be evident that widespread epidemics of wound infections may be explained by a general and continuing distribution of the offending bacteria and cannot be explained always by incidental breaks in the aseptic technique routinely used. Frequently, when such an epidemic of wound infections has occurred, the aseptic ritual in the unfortunate hospital has been restudied and made more rigid, even when defects have not been demonstrated. During the time required for such a study, the epidemic of respiratory infections and the resultant air contamination may have subsided and the infection rate may have returned to the normally low level. Credit for control of the wound infections has then been attributed to the additional precautions instituted.

It is generally recognized that postoperative infections in clean wounds occur frequently, that they are caused predominantly by staphylococci, that the organisms are widely distributed, and that the respiratory tract is the usual reservoir. It is less generally recognized that these organisms can be recovered by sedimentation from the air of most closed areas that contain human beings. The effectiveness of ultraviolet radiation (2,537 A) in killing rapidly such bacteria either in the air or on exposed surfaces is pertinent. A communication by Hart in this issue of THE JOURNAL, page 1019, describes experience with ultraviolet radiation at Duke University over a period of three decades.

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[1] Lister, J.: On Antiseptic Principle in Practice of Surgery, Lancet 2:353, 1867.

The control of epidemics of gastrointestinal infections by elimination of bacterial spread through contaminated water and food is recognized. In contrast to the intake of fluid and food, which is intermittent and can be deferred until rendered safe, the intake and exchange of air is a continuous process. Fortunately, the reservoir of air in which we live and breathe is relatively free of pathogenic bacteria, except in occupied closed areas. Here the degree and type of such contamination depend on the concentration of occupants who are carriers, the degree of their respiratory tract contamination, the propulsive forces that put the organisms into the air, the frequency of air changes, and the favorable or deleterious influences that affect the bacterial environment. The lethal value of ultraviolet sunlight against pathogenic bacteria and the purity of the air in the "wide open spaces" have long been recognized. It is not difficult to supply the operating rooms with air free of pathogenic bacteria. This is accomplished by taking in air that is relatively free of bacteria and removing the rest by washing and by mechanical and electrostatic filtration. However, subsequent pollution of this clean air in the occupied room with the pathogenic flora of the respiratory tracts of the occupants is difficult, if not impossible, to prevent. Such pollution can be held to a low level by limiting occupancy, by reducing propulsive forces, by more adequate masking, and by reduction of the bacterial build-up by frequent air changes. Even with these precautions, the organisms remaining in the air, if highly pathogenic, may cause wound infections of varying degrees of severity.

Continuous exposure of the operating room to an adequate intensity of ultraviolet radiation has been in daily use in the Duke Hospital for over 24 years and in as many as 15 operating rooms at a time. The viable bacteria on exposed surfaces and those settling from the air have been held to a low level. "Unexplained infections" in clean wounds have been reduced to a low percentage. This has been accomplished without serious or permanent injury to patient or personnel, even during the longest operations or after almost daily exposures of persons for more than two decades. The only protection used is shading of the skin and eyes, an insignificant handicap during an operative procedure. Although the source of the offending organisms is predominantly the respiratory tracts of the occupants of the operating room, control of the air route of spread is equally effective regardless of the source of the organisms, whether it is the respiratory tracts, air-conditioning system, blankets, linens, shoes, the floor of the operating room, or distant parts of the hospital. Consideration of this phase of bacterial control of the operating room seems pertinent.

COUNSEL TO AUTHORS

For many years the advertising pages have carried a column each week entitled "Suggestions for Contributors." Like a number of documents that appear unchanged decade after decade the suggestions were probably seldom read even by those who might have profited by doing so. A major revision has been made in the column in this issue. It is hoped that those who wish to prepare a manuscript for THE JOURNAL will take a moment to read what has been restyled as "Counsel to Authors." Special attention is directed to the paragraph beginning "Manuscripts . . ." which mentions the newly prepared pamphlet, "Suggestions for Authors of Articles Submitted to THE JOURNAL of the American Medical Association." A copy of the new suggestions may be obtained on request. It should prove helpful to the author.

THE DOCTOR ABROAD

At the turn of the century a significant number of physicians pursued postgraduate training in the medical centers of Europe, especially Austria and Germany. A smaller number of physicians visited the continent or other lands outside of America each year, attracted solely by the amenities of travel. In the second half of this century the reverse will most likely hold. The majority of physicians who travel abroad in 1960 will be pleasure-bound. Their activities will include a minimum of professional liaison. Only a smattering will undertake full-time postgraduate study. It is assumed that physicians in this category will do an excellent job of promoting understanding between other lands and the United States. It is to the traveling physician in the first category that a word of encouragement may be opportune.

The encouragement is to do more and not to do less while abroad. The opportunities to enrich one's experience as well as to foster better international relationships should not be overlooked. Behrman has emphasized in his letter to the editor, on page 1082, in this issue that physicians from the United States usually are welcome in any hospital, medical school, or doctor's office about the world. In most instances their presence is deeply appreciated, and, before many minutes have passed, the value of the exchange begins to be sensed. If one wishes to go further and initiate a one-way exchange, this also may prove to be highly enlightening as well as most self-satisfying.

Immediately after World War II, when critical drug items such as penicillin were short in supply, even small quantities of this drug were welcome abroad. The need for antibiotics, steroids, or other useful drugs probably is not critical in many areas at the present time. There are lands, however, particularly in the poorly developed areas of the world, where drugs still are critically short in supply and any quantity will be welcome. Another avenue for appreciation is the dispatch of books and periodicals. There are a number of areas in the world that are deficient in current monographs and textbooks as well as current periodicals. If contact is established with one or more physicians, most likely there are pieces of equipment, books, or periodicals in your office that might be sent abroad on your return to the United States that would be appreciated to the utmost and would strengthen mutual ties. The opportunity to support a one-man Marshall plan, patterned after the experience of Dr. Behrman, should not be overlooked. Areas that are in need of medical strength, spiritually and substance-wise, include most of the communities outside of the large population centers of the free world.

THE FOREIGN-SCHOOLED INTERN

The progressive increase each year in the number of interns who have received their formal professional education in a foreign land is of great general concern. The acceptance on the house staff of an intern educated outside of North America places responsibility on those who are answerable for the training program that is not appreciated universally. Newsworthy examples of substandard performance which expose our vulnerability to criticism of the current system of exploiting the outlander in many of our hospitals are featured in the public press from time to time. The unfortunate experience in New York City last fall which involved an intern from India and a British actor may be cited.

Whatever the goal of the intern, the hospital needs him and is dependent on the service he renders and is happiest when he is a graduate of an American medical school. Great effort is expended ordinarily by the medical staff in the education of the intern in the teaching hospital allied with a medical school. This effort is not as predictable in the nonaffiliated hospital. It is generally agreed, however, that the greater the industry of the visiting staff directed toward the intern training program the better the program and the better the patient care. One might speculate that an approximate correlation exists between the hours of thought and guidance of the internship by the professional staff and the number of fourth-year students who apply for that internship.

The distribution of foreign-born interns in American hospitals does not follow such a predictable pattern. The internships most highly desired by American graduates usually enroll the smallest number of foreign graduates. Hospitals with inferior or mediocre intern training programs enroll the largest number of foreign-born interns. The situation is truly deplorable in some hospitals. The responsibility for this state of affairs can be assigned only to a disinterested visiting staff. Instead of enlarging his professional experience, the foreign-born intern in such a situation may be assigned duties commensurate with a medical technologist. Even more frightening, he may be assigned complete responsibility for the medical care of a large number of patients; a responsibility for which he is often totally unprepared.

It is only fair to note, however, that in unusual circumstances the foreign intern may be exposed to a planned program of learning under the careful supervision of a director of house staff education, complemented by the understanding instruction of an enlightened portion of the attending staff. The educational opportunities and the professional responsibilities in this instance approach those offered by a medical school affiliated hospital. But even in such an institution, a truly valuable experience depends on a fairly satisfactory reading, writing, and speaking knowledge of the English language. Without this, it will be virtually impossible for the intern to gain the necessary familiarity with American customs as well as the professional knowledge and professional techniques which are the principal goals of the experience. In the absence of communicative skills even intellectual proficiency, industry, and dedication are not adequate to carry the foreign graduate toward the goal.

What is the result of this broad deficiency and deep mediocrity? The foreign-born intern is often least aware of the shortcomings of the internship and may appear thoroughly satisfied. It is a new experience for him, and if he fails to gain professional attainments, at least he is rewarded by the opportunity to live in a prosperous land, to consume good food, to dress well, to attend the latest movies, and to watch television. Unfortunately these should not be the zenith of attainment in themselves. The foreign graduate should be accepted for the same purpose as our American interns. He should be qualified according to standards established by the Educational Council for Foreign Medical Graduates. The hospital that accepts him must provide the same educational experience offered his American counterpart. The hospital should not accept him as a servant. The visiting staff cannot be allowed to shirk its responsibility to him, nor can he be allowed to overlook the responsibility to his native land, the fulfillment of which was the basic purpose for his admission to America and to an American hospital. It is the breadth of clinical knowledge gained here that will permit him to serve his people better upon his return. This fact cannot be forgotten. Should he decide to remain in America and practice, undoubtedly we gain. But it is usually at the expense of his own people, who in the majority of instances need his medical skill desperately. The magnitude of this problem increases yearly. Organized medicine has given much thought to these matters. Some progress has been made; much more progress is imperative.

COMMITTEE ON MEDICAL RATING OF PHYSICAL IMPAIRMENT

GUIDES TO THE EVALUATION OF PERMANENT IMPAIRMENT

THE CARDIOVASCULAR SYSTEM

Preface

Evaluation or rating of permanent disability has long been recognized as an important and complex subject. In the past much confusion has resulted from inadequate understanding by physicians and others of (*a*) the scope of medical responsibility in the evaluation of permanent disability; and (*b*) the difference between "permanent disability" and "permanent impairment."

It is vitally important for every physician to be aware of his proper role in the evaluation of permanent disability under any private or public program for the disabled. It is equally important for him to have the necessary authoritative material to assist him in competently fulfilling his particular responsibility—the evaluation of permanent impairment. It is the purpose of this and other reports of the Committee on Medical Rating of Physical Impairment to correct a past confusion of terms and to provide a series of practical guides to the evaluation of various types of permanent impairments.

The following explanations of generally used terms in programs for the disabled will suffice, for all practical purposes.

1. *Permanent Disability.*—This is not a purely medical condition. A patient is "permanently disabled" or "under a permanent disability" when his actual or presumed ability to engage in gainful activity is reduced or absent because of "impairment" and no fundamental or marked change can be expected in the future.

2. *Permanent Impairment.*—This is a purely medical condition. Permanent impairment is any anatomic or functional abnormality or loss after maximum medical rehabilitation has been achieved and which abnormality or loss the physician considers stable or nonprogressive at the time evaluation is made. It is always a basic consideration in the evaluation of permanent disability. It should be remembered, however, that permanent impairment is a contributing factor to, but not necessarily an indication of, the extent of a patient's permanent disability.

3. *Evaluation (Rating) of Permanent Disability.*—This is an administrative, not a medical, responsibility and function. Evaluation of permanent disability is an appraisal of the patient's present and probable future ability to engage in gainful activity as it is affected by nonmedical factors such as age, sex, education, and economic and social environment, and the medical factor—permanent impairment. Nonmedical factors have proved extremely difficult to measure. For this reason permanent impairment is, in fact, the sole or real criterion of permanent disability far more often than is readily acknowledged. A determination of permanent disability is an administrative decision about the patient's entitlement.

4. *Evaluation (Rating) of Permanent Impairment.*—This is a function that physicians alone are competent to perform. Evaluation of permanent impairment defines the scope of medical responsibility and therefore represents the physician's role in the evaluation of permanent disability. Evaluation of permanent impairment is an appraisal of the nature and extent of the patient's illness or injury as it affects his personal efficiency in the activities of daily living. These activities are self-care, communication, normal living postures, ambulation, elevation, traveling, and nonspecialized hand activities. It is not and never can be the duty of physicians to evaluate the social and economic effects of permanent impairment. These effects must be evaluated by administrators in making determinations of permanent disability.

Competent evaluation of permanent impairment requires adequate and complete medical examination, accurate objective measurement of function, and avoidance of subjective impressions and nonmedical factors such as the patient's age, sex, or employability.

The Committee on Medical Rating of Physical Impairment believes that permanent impairment cannot vary because of the circumstances of its occurrence or the geographical location of the patient at the time. Furthermore, unlike disability, permanent impairment can be measured with a reasonable degree of accuracy and uniformity on the basis of impaired function as evidenced by loss of structural integrity, pathological findings, or pain substantiated by clinical examination.

Members of the Committee on Medical Rating of Physical Impairment are Drs. Raymond M. McKeown, Coos Bay, Ore., Chairman; George F. Gsell, Wichita, Kan.; Henry H. Kessler, Newark, N. J.; Quenton W. Mack, Boise, Idaho; and O. A. Sander, Milwaukee. Mr. George W. Cooley of Chicago is secretary.

Consultants in the preparation of this guide were Drs. David I. Abramson, Chicago; Lewis H. Bronstein, New York City; Richard J. Clark, Winchester, Mass.; S. Charles Franco, New York City; Leonard J. Goldwater, New York City; Hugh Montgomery, Philadelphia; William A. Leff, Newark, N. J.; Thomas W. Parkin, Rochester, Minn.; Oglesby Paul, Chicago; Donal R. Sparkman, Seattle; William D. Stroud, Philadelphia (deceased); James V. Warren, Galveston, Texas; and J. Allen Yager, Paterson, N. J.; and Mrs. Marjorie W. Grigsby, Evanston, Ill.

The Committee is familiar with the various formulas developed in the past for use in evaluation of permanent disability. These formulas are usually administrative devices which equate specific medical criteria to specific percentages of permanent partial or total disability (loss of working or earning capacity). From the medical standpoint the medical criteria may undeniably represent various anatomic or functional impairments. However, it is unrealistic to presume that many of these impairments, especially those of a minor nature, will necessarily at some time result in disability. These administrative devices are not generally available to physicians and in any event would not be useful in making sound evaluations of permanent impairment. On the other hand, although a number of valuable contributions have been made in the past, the Committee found no comprehensive practical system of the type necessary for the evaluation of permanent impairment by individual body systems or of the whole man. For this reason the Committee has undertaken to prepare a series of guides. The Committee has been greatly assisted in its work by the outstanding consultants whose names appear in connection with the appropriate guides.

Three guides are now available. The first, dealing with the extremities and back, was published as a special edition of the Feb. 15, 1958, issue of The Journal; the second, concerned with the visual system, was published as a special article in the Sept. 27, 1958, issue of The Journal. This third guide deals with the cardiovascular system.

All of the guides have been developed after careful study of the literature and of the views of recognized authorities and will be reviewed periodically to insure their continuing value as advances in medical knowledge and technique occur.

Each guide contains recommended percentage values related to the criteria provided. The use of numerical values is preferred because of difficulty in communication and variability in interpretation of such terms as "slight," "marked," and "moderate." Such values provide a practical means of expressing and calculating the extent of permanent impairment and encourage accurate, equitable, and uniform evaluation. Methods of calculating impairment are uniform, explained in detail with examples, and require a minimum of computation. Generally, when a single impairment is involved, the percentage value may be read directly from the text or transposed to a relative value of a unit of the body or of the whole man by referring to appropriate tables.

When two or more impairments are involved, however, the value of each impairment must be ascertained and transposed to a common denominator, such as the whole man. Thereafter these values must be combined. A combined values table is provided by which any combination of impairments may be easily found. The method generally used to combine various impairments is based on the principle that each impairment acts not on the whole part but on the portion which remains after the preceding impairment has acted. For purposes of computation, the source and chronology of the impairment values are immaterial.

After the values of all impairments involved have been computed and transposed to a common denominator, the final impairment value, whether the result of single or of combined impairments, is expressed in terms of the nearest 5%.

Introduction

Permanent impairment in varying degrees may result from any anatomic or functional deviation from normal in the cardiovascular system. The purpose of this guide is to assist physicians by providing criteria and methods for determining the degree of such impairment in terms of the whole man.

Evaluation of cardiovascular impairment involves special considerations and poses certain problems which are not generally encountered in evaluating other impairments. For these reasons the criteria provided in this guide must be general, yet reasonably specific, and withal not so complex as to discourage general use.

Special Considerations.—Permanent impairment in a cardiovascular context may be described as that condition which persists after maximum medical and surgical therapeusis and rehabilitation, and after a reasonable period has elapsed to permit maximum development of collateral circulation and other adjustments of nature after an acute insult. For example, a period of not less than six months should elapse before determination of permanent impairment after an acute myocardial infarction. In case of operation for rheumatic or congenital heart disease, the period should be at least one year after operation.

Furthermore, it must be recognized that the degree of permanent cardiovascular impairment is not static. Unlike certain other types of impairments, a constantly changing process is usually involved. For this reason all findings should be subject to review and the patient reevaluated for possible deterioration or improvement at intervals of six months to one year, depending on circumstances. This is also necessary because of the potential benefits to patients from newer therapeutic methods as they are developed in this rapidly changing field.

One of the problems in the evaluation of cardiovascular impairment is the frequent disparity between objective findings and subjective symptoms. For instance, a patient with coronary artery disease may appear completely normal on examination, including electrocardiogram and x-ray, yet he may be severely impaired by angina pectoris. At the other extreme is the patient with a loud murmur, moderately severe cardiac enlargement, and a bizarrely abnormal electrocardiogram; yet this patient may be able to perform his accustomed activities in comfort despite these apparently unfavorable findings.

It must be emphasized that the presence of symptoms or even signs suggesting heart disease does not necessarily indicate a pathological process of that organ. These manifestations may be purely psychological in origin. Moreover the presence of organic heart disease may render a patient more susceptible to the development of symptoms of a psychological nature. In view of these considerations, the paramount importance of a detailed and critical history is clear since it may serve as the principal or even the only basis for the evaluation of permanent impairment.

Method of Evaluation.—Evaluation of cardiovascular impairment is usually possible through sound clinical judgment based on a history, examination, and a minimum of laboratory aids.

It would be highly desirable if specific objective tests of cardiovascular function were available, from which relative impairment could be directly determined. If, for example, a test of a patient's physiological capacity could be matched with the energy requirements of various activities, a decision regarding his abilities might be easily reached. Unfortunately, the available tests do not provide such a simple solution. The performance of exercise tests provides an excellent opportunity for the physician to observe his patient under the stress of physical activity and may aid in diagnosis. In some instances, such tests lead to the discovery of excessive restriction of the patient's activity. It should be remembered, however, that the patient's performance may be importantly modified by his emotional approach and that evaluation of the test result is made difficult by considerable individual variations in training and physical ability. Physiological function tests, although of limited value at present, offer a fertile field for research and development. They supplement but do not substitute for the physician's clinical evaluation.

Classification.—Before classifying any patient, the physician must establish as accurately as possible a firm etiological,anatomic, and physiological diagnosis, supported by appropriate signs and symptoms as set forth in accepted criteria. As a result of a carefully obtained history, a thorough physical examination, and the use of appropriate laboratory aids, the physician should be able to classify a patient within the categories listed below and thereafter determine the percentage of impairment of the whole man.

For practical purposes, three categories have been established: (*a*) heart disease, (*b*) hypertensive vascular disease, and (*c*) vascular diseases affecting the extremities.

Each category is divided into a series of classes, each with its respective subjective and objective clinical findings and corresponding percentages of impairment.

When the clinical findings are such that a patient may not be classified in a single one of the above categories, evaluation of impairment in accordance with each of the appropriate categories should be made and the corresponding percentages of impairment noted. These values are then combined to obtain the percentage of impairment of the whole man contributed by the cardiovascular system.

Reports.—When making oral or written reports, the physician should explain and substantiate his conclusions about the patient's status. He should also clearly indicate that this information represents his findings and conclusions as of the date evaluation is made. A detailed history, complete physical examination findings, laboratory examination and reports, diagnoses, classification, and the resulting impairment value should be reported.

HEART DISEASE

Permanent impairment due to heart disease most commonly results from (1) failure of myocardial function leading to congestive heart failure; (2) impairment of coronary circulatory function resulting in angina pectoris, coronary insufficiency, coronary occlusion, or myocardial infarction and its complications; or (3) a combination of these.

The etiological diagnoses most commonly encountered are congenital, rheumatic, arteriosclerotic (coronary), hypertensive, syphilitic, and pulmonic (cor pulmonale) heart disease. In addition, it is recognized that in rare instances neurocirculatory asthenia (effort syndrome) and arrhythmias, occurring without demonstrable organic disease, may produce permanent impairment.

This category is divided into five classes, each with percentage values representing the impairment of the patient as a whole man. Classes 1 through 4 apply to patients with organic heart disease ranging from the asymptomatic (class 1) to the severely impaired (class 4). These four classes are adapted from the functional and therapeutic classifications of the American Heart Association. The fifth class, class 0, applies to patients with nonorganic heart disturbances.

Class 1—Impairment of Whole Man, 0-15%.—A patient belongs in class 1 when (*a*) organic heart disease exists but without resulting symptoms; (*b*) walking, climbing stairs freely, and the performance of the usual activities of daily living do not produce symptoms; (*c*) prolonged exertion, emotional stress, hurrying, hill-climbing, recreation (prophylactic restriction of activity such as strenuous competitive sport does not exclude a patient from this class), or similar activities do not produce symptoms; and (*d*) signs of congestive heart failure are not present.

Example 1: On routine chest survey, calcification was found in the patient's pericardium. Clinical examination revealed no evidence of other cardiac impairment and the patient was asymptomatic.

Diagnoses: Etiological: Unknown.
Anatomic: Calcified pericardium.
Physiological: Normal sinus rhythm; no cardiac insufficiency.
Impairment: 0% impairment of the whole man.

Example 2: A 25-year-old man has a definite history of rheumatic fever, presenting a grade 3 apical systolic murmur. Despite these findings he is asymptomatic and leads a normal life without limitation of activity.

Diagnoses: Etiological: Rheumatic fever, inactive.
Anatomic: Mitral insufficiency; no cardiac enlargement.
Physiological: Normal sinus rhythm; no cardiac insufficiency.
Impairment: 5% impairment of the whole man.

Example 3: The patient is a 50-year-old man who sustained a confirmed posterior myocardial infarction one year ago and made a good recovery. He has continued to show a fixed electrocardiographic pattern of the old infarct but has had no further angina, dyspnea, or other symptoms. He is able to carry on normal life activities, although he avoids excesses of exertion on the advice of his physician.

Diagnoses: Etiological: Atherosclerosis of the coronary arteries.
Anatomic: Healed myocardial infarction.
Physiological: Normal sinus rhythm; no cardiac insufficiency.
Impairment: 15% impairment of the whole man.

Class 2—Impairment of Whole Man, 20-40%.—A patient belongs in class 2 when (*a*) organic heart disease exists, but without resulting symptoms at rest; (*b*) walking freely on the level, climbing at least one flight of stairs, and the performance of the usual activities of daily living do not produce symptoms; (*c*) prolonged exertion, emotional stress, hurrying, hill-climbing, recreation, or similar activities produce symptoms; and (*d*) signs of congestive heart failure are not present.

Example 1: A 40-year-old man has clear evidence of rheumatic heart disease and mitral stenosis, with slight cardiac enlargement and atrial fibrillation. Two years ago he developed increasing dyspnea on exertion and had several episodes of paroxysmal nocturnal dyspnea. One year ago a mitral valvuloplasty was performed with highly successful results and marked improvement. There has been no further nocturnal dyspnea. Dyspnea on exertion has decreased until it occurs only with hurrying up two flights of stairs, hill-climbing, or fast walking of distances over a mile. He is continuing on a maintenance dose of digitalis.

Diagnoses: Etiological: Rheumatic fever, inactive.
Anatomic: Mitral stenosis, enlargement of heart; mitral valvuloplasty, postoperative.
Physiological: Atrial fibrillation; no cardiac insufficiency.
Impairment: 25% impairment of the whole man.

Example 2: A 54-year-old man two years ago experienced episodes of recurrent chest pain due to severe coronary insufficiency. After a three-month period of hospitalization and rest the symptoms largely abated and he was able to resume most of his usual activities. For the next six months typical angina occurred with walking more than a quarter of a mile and with stair climbing. Conditions improved, however, and for the past year he has been able to lead a normal life and to play golf. In this latter period typical angina and dyspnea have occurred only occasionally with emotional stress or hurrying.

Diagnoses: Etiological: Arteriosclerosis of coronary arteries.
Anatomic: Coronary sclerosis.
Physiological: Angina syndrome; normal sinus rhythm; no cardiac insufficiency.
Impairment: 35% impairment of the whole man.

Class 3—Impairment of Whole Man, 50-70%.—A patient belongs in class 3 when (*a*) organic heart disease exists but without resulting symptoms at rest; (*b*) walking more than one or two blocks on the level, climbing one flight of ordinary stairs, or the performance of the usual activities of daily living produce symptoms; (*c*) emotional stress, hurrying, hill-climbing, recreation, or similar activities produce symptoms; and (*d*) signs of congestive heart failure, if present, are usually relieved by therapy.

Example 1: A 50-year-old man has evidence of free aortic regurgitation and moderate cardiac enlargement. There was a history of syphilis for which full penicillin therapy had been given two years ago. He had past episodes of nocturnal dyspnea and intermittent ankle edema, but these had been held in abeyance during the past year since the institution of digitalis therapy, a low-sodium regimen, and occasional diuretics. Despite this he continues to have dyspnea on climbing one flight of stairs or on walking two blocks on the level.

Diagnoses: Etiological: Syphilis—inactive.
Anatomic: Enlarged heart, aortic insufficiency.
Physiological: Normal sinus rhythm, cardiac insufficiency.
Impairment: 60% impairment of the whole man.

Example 2: A 60-year-old man sustained attacks of myocardial infarction five years ago and again two years ago. Since the latter he has developed increasing dyspnea on exertion and typical angina on any special activity. Because of difficulties in stair climbing he has moved to a first-floor apartment. He is unable to walk more than one or two blocks slowly without dyspnea or chest pain despite fully adequate treatment including diuretic and digitalis therapy.

Diagnoses: Etiological: Arteriosclerosis of the coronary arteries.
Anatomic: Sclerosis of the coronary arteries, infarction of the myocardium.
Physiological: Anginal syndrome, normal sinus rhythm, cardiac insufficiency.

Impairment: 70% impairment of the whole man.

Class 4—Impairment of Whole Man, 80-95%.—A patient belongs in class 4 when (*a*) organic heart disease exists with symptoms even at rest; (*b*) the performance of any of the activities of daily living beyond the personal toilet or its equivalent produces increased discomfort; (*c*) symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest; and (*d*) signs of congestive heart failure, if present, are usually resistant to therapy.

Example 1: A 42-year-old man has had rheumatic heart disease since the age of 12 years. He was excluded from competitive sports in high school and college because of mitral stenosis and insufficiency. He had no symptoms until three years ago, when he noted dyspnea on exertion, palpitation, and periodic edema of the ankles. Physical examination revealed atrial fibrillation, cardiac enlargement, double mitral valve murmurs, and congestion of the lungs. He responded well to therapy with digitalis, diuretics, and a salt-free diet. Two years ago he developed numerous episodes of nocturnal dyspnea and hemoptysis. The congestive failure became more difficult to control. In addition to maintenance therapy with digitalis, he required parenteral administration of mercurials two or three times weekly. For the past 10 months his activities about the house have been limited to those of personal care and walking only from one room to the next.

Diagnoses: Etiological: Rheumatic fever, inactive.
Anatomic: Mitral stenosis, mitral insufficiency, enlarged heart.
Physiological: Atrial fibrillation, cardiac insufficiency.

Impairment: 95% impairment of the whole man.

This classification (classes 1-4), without examples, is shown in table 1.

Table 1.—*Classes of Organic Heart Disease*

Class 1 (0-15% Impairment)	Class 2 (20-40% Impairment)	Class 3 (50-70% Impairment)	Class 4 (80-95% Impairment)
Organic heart disease exists, but without resulting symptoms	Organic heart disease exists, but without resulting symptoms at rest	Organic heart disease exists, but without resulting symptoms at rest	Organic heart disease exists with symptoms even at rest
Walking, climbing stairs freely, and the performance of the usual activities of daily living do not produce symptoms	Walking freely on the level, climbing at least one flight of stairs, and the performance of the usual activities of daily living do not produce symptoms	Walking more than one or two blocks on the level, climbing one flight of ordinary stairs, or the performance of the usual activities of daily living produce symptoms	The performance of any of the activities of daily living beyond the personal toilet or its equivalent produces increased discomfort
Prolonged exertion, emotional stress, hurrying, hill-climbing, recreation,* or similar activities do not produce symptoms	Prolonged exertion, emotional stress, hurrying, hill-climbing, recreation, or similar activities produce symptoms	Emotional stress, hurrying, hill-climbing, recreation, or similar activities produce symptoms	Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest
Signs of congestive heart failure are not present	Signs of congestive heart failure are not present	Signs of congestive heart failure may be present, and if so, are usually relieved by therapy	Signs of congestive heart failure, if present, are usually resistant to therapy

* Prophylactic restriction of activity such as strenuous competitive sports does not exclude a patient from class 1.

Class 0—Nonorganic Heart Disturbances, Impairment of Whole Man, 0-10%.—Depending on their duration and frequency, arrythmias such as (1) paroxysmal atrial (auricular) flutter or fibrillation or (2) paroxysmal supraventricular tachycardia may produce impairment, but persons with these types must be placed in class 0. Premature beats of various types or sinoauricular tachycardia are considered nonimpairing when found alone.

Note: Neurocirculatory asthenia, cardiac anxiety neurosis, or effort syndrome, characterized by a group of symptoms including dyspnea, palpitation, chest pains, dizziness, exhaustion, and nervousness aggravated by mental or physical strain are recognized as significant entities which may, although rarely, cause impairment. When the symptoms are of sufficient severity to interfere with the activities of daily living, the problem is neuropsychiatric and for this reason no rating is given here.

HYPERTENSIVE VASCULAR DISEASE

Before classifying a patient in the category of hypertensive vascular disease, the physician should make every effort to avoid variables of measurement, by repeated examinations of arterial pressure, and to ascertain the etiological type of hypertension present.

Hypertensive vascular disease does not necessarily exist or develop when a patient exhibits transient or irregular episodes of elevated arterial pressure; these frequently are associated with increased heart rate, with some obvious emotional stimulus or environmental factor, or with signs or symptoms of hyperactivity.

Hypertensive vascular disease is assumed to be present when diastolic pressure is repeatedly in excess of 100 mm. Hg. Diastolic blood pressure readings less than 100 mm. Hg occurring as the result of therapy or intercurrent complications do not exclude a patient from this category.

Class 1—Impairment of Whole Man, 0-15%.—A patient with hypertensive vascular disease belongs in class 1 when diastolic pressure readings are repeatedly in excess of 100 mm. Hg and examination reveals none of the following findings: (*a*) abnormalities of urinalysis and urinary function tests, (*b*) history of hypertensive cerebrovascular damage, (*c*) evidence of left ventricular hypertrophy, or (*d*) hypertensive abnormalities of the optic fundus (except minimal narrowing or sclerosis of arterioles).

Class 2—Impairment of Whole Man, 20-40%.—A patient with hypertensive vascular disease belongs in class 2 when diastolic pressure readings are or have been regularly in excess of 100 mm. Hg and examination reveals any one of the following findings: (*a*) proteinuria and abnormalities in the urinary sediment but no impairment of renal function, (*b*) history of hypertensive cerebrovascular damage without residuals, (*c*) evidence of left ventricular hypertrophy, or (*d*) definite hypertensive changes in the retinal arterioles, with or without hemorrhages and exudates.

Class 3—Impairment of Whole Man, 50-70%.—A patient with hypertensive vascular disease belongs in class 3 when diastolic pressure readings are consistently in excess of 100 mm. Hg and examination reveals any two of the following findings: (*a*) diastolic pressure readings usually in excess of 120 mm. Hg, (*b*) proteinuria and abnormalities in the urinary sediment, with evidence of impaired renal function, (*c*) hypertensive cerebrovascular damage with permanent neurological residuals, (*d*) left ventricular hypertrophy but no congestive heart failure, or (*e*) retinopathy with definite hypertensive changes in the arterioles, with or without hemorrhages and exudates.

Class 4—Impairment of Whole Man, 80-95%.—A patient with hypertensive vascular disease belongs in class 4 when diastolic pressure readings are consistently in excess of 100 mm. Hg and examination reveals any two of the following findings: (*a*) diastolic pressure readings usually in the range of 140 mm. Hg or more, (*b*) proteinuria and abnormalities in the urinary sediment, with impaired renal function and evidence of nitrogen retention, (*c*) hypertensive cerebrovascular damage with permanent neurological residuals, (*d*) left ventricular hypertrophy with or without congestive heart failure, or (*e*) retinopathy as manifested by hypertensive changes in the arterioles, retina, or optic nerve.

This classification is shown in table 2.

VASCULAR DISEASES AFFECTING THE EXTREMITIES

Permanent impairment due to peripheral vascular disorders most commonly results from (1) diseases of the arteries that reduce blood flow and lead to one or more of the following: intermittent claudication, pain at rest, minor trophic changes, ulceration, gangrene, or loss of extremity; (2) diseases of the veins, resulting in one or more of the following: pain, edema, induration, stasis dermatitis, or ulceration; or (3) disorders of the lymphatics, leading to chronic lymphedema or elephantiasis.

The etiological factors most commonly encountered in patients with the arterial disorders are arteriosclerosis, trauma, and inflammatory lesions such as thromboangiitis obliterans. The venous system is most frequently affected by varicosities and thrombotic states. Diseases of the lymphatic system most frequently causing impairment are obstructive lesions of an inflammatory or neoplastic origin.

This category is divided into five classes, from the minimal nonimpairing (class 1) to the most severely impairing (class 5). Percentage values representing the impairment of the patient as a whole man are assigned to each class.

It is assumed that prior to classification a specific diagnosis of vascular disease has been established according to conventional criteria. The use of special and frequently simple tests of vascular function is often necessary, and the physician is referred to the standard texts for a discussion of these methods.

Since the classification of the patient depends on the severity and extent of the lesions, only those factors indicating these are used in the classification which follows.

The percentage of permanent impairment of any patient in this category should be ascertained by placing him in the appropriate class and determining the corresponding percentage of permanent impairment of the whole man. This also applies to those rare cases in which vascular disease may restrict joint motion.

An exception is made, however, when amputation due to peripheral vascular disease is involved. In these cases an additional percentage of permanent impairment is to be allowed. The percentage of permanent impairment due to amputation is determined in accordance with the amputation schedule shown in table 4, which has been taken from "A Guide to the Evaluation of Permanent Impairment of the Back and Extremities." The amputation percentage value and the classification percentage value are then combined, by means of the combined values table.

Class 1–Impairment of Whole Man, 0%.—A patient with vascular disease (or diseases) belongs in class 1 if (*a*) he experiences neither intermittent claudication nor pain at rest and (*b*) he experiences only transient edema.

Note: It is understood that the disease is not considered impairing if only the following findings are present: (*a*) loss of pulses; (*b*) minimal loss of subcutaneous tissue of fingertips; (*c*) calcification of arteries as detected by x-ray examination; and (*d*) asymptomatic dilatation of arteries (including painless aneurysms not amenable to surgery) or of veins, resulting in no curtailment of activity.

TABLE 2.—*Classes of Hypertensive Vascular Disease*

Class 1 (0-15% Impairment)	Class 2 (20-40% Impairment)	Class 3 (50-70% Impairment)	Class 4 (80-95% Impairment)
Hypertensive vascular disease exists, diastolic pressure readings are repeatedly in excess of 100 mm. Hg, and examination reveals none of the following findings	Hypertensive vascular disease exists, diastolic pressure readings are or have been repeatedly in excess of 100 mm. Hg, and examination reveals any one of the following findings	Hypertensive vascular disease exists, diastolic pressure readings are consistently in excess of 100 mm. Hg, and examination reveals any two of the following findings	Hypertensive vascular disease exists, diastolic pressure readings are consistently in excess of 100 mm. Hg, and examination reveals any two of the following findings
		Diastolic pressure readings usually in excess of 120 mm. Hg	Diastolic pressure readings usually in excess of 140 mm. Hg
Abnormalities of urinalysis and urinary function tests	Proteinuria and abnormalities in the urinary sediment and no impairment of renal function	Proteinuria and abnormalities in the urinary sediment with evidence of impaired renal function	Proteinuria and abnormalities in the urinary sediment with impaired renal function and evidence of nitrogen retention
History of hypertensive cerebrovascular damage	History of hypertensive cerebrovascular damage without residuals	Hypertensive cerebrovascular damage with permanent neurological residuals	Hypertensive cerebrovascular damage with permanent neurological residuals
Evidence of left ventricular hypertrophy	Evidence of left ventricular hypertrophy	Left ventricular hypertrophy but no congestive heart failure	Left ventricular hypertrophy, with or without congestive heart failure
Hypertensive abnormalities of the optic fundus (except minimal narrowing or sclerosis of arterioles)	Definite hypertensive changes in the retinal arterioles, with or without hemorrhages and exudates	Retinopathy with definite hypertensive changes in arterioles, with or without hemorrhages and exudates	Retinopathy as manifested by hypertensive changes in the arterioles, retina, or optic nerve

EXAMPLE 1: A 27-year-old woman had ileofemoral phlebitis after childbirth. The leg became painful on a regimen including anticoagulants, and for several months she had to wear an elastic stocking to prevent moderate edema. Now she notices a little swelling of the ankle at the end of the day. This disappears by morning. She no longer uses the elastic support.

Impairment: 0% impairment of the whole man.

Class 2–Impairment of Whole Man, 5-25%.—A patient with vascular disease (or diseases) belongs in class 2 when any one of the following findings exists: (*a*) intermittent claudication occurring on walking at least 100 yd. at an average pace, (*b*) vascular damage as evidenced by physical signs such as healed painless stump of an amputated single digit with evidence of persistent vascular disease or healed ulcer, or (*c*) persistent edema of a moderate degree, incompletely controlled by elastic supports.

EXAMPLE 1: Two years ago a 53-year-old man experienced sudden pain in the left calf while walking. For several months the left leg was cooler than the right. The left superficial femoral artery was found to be occluded. For the past year he has been able to walk only 200 yd. before pain occurs. As soon as the patient stops walking, relief is obtained. There are no other symptoms.

Impairment: 15% impairment of the whole man.

EXAMPLE 2: Several years ago three fingers of a woman's left hand became painful, cool, and alternately blanched and cyanotic. The middle finger was then injured and became infected and painful. The tip of the finger became necrotic and therefore the distal phalanx was amputated. Her recovery was uneventful and there has been no progression in the symptoms.

Impairment: 19% impairment of the whole man; 15% contributed by class 2 vascular disease and 5% contributed by amputation of distal phalanx of middle finger (15 combined with 5 is 19).

Class 3–Impairment of Whole Man, 25-50%.—A patient with vascular disease (or diseases) belongs in class 3 when any one of the following findings exists: (*a*) intermittent claudication occurring on walking as little as 25 yd. and no more than 100 yd. at an average pace, (*b*) vascular damage as evidenced by physical signs such as healed amputation of two or more digits of one extremity with evidence of persistent vascular disease or persistent superficial ulceration, or (*c*) marked edema which is only partially controlled by elastic supports.

EXAMPLE 1: Eight months ago a 45-year-old man with known diabetes mellitus of five years' duration developed a painful inflamed callus under the first metatarsophalangeal joint of the right foot. Purulent material was removed from under the callus and the pain was relieved. A sinus formed, however, and is only slowly improving. No pulse can be felt at the ankle. A vasodilation test shows that the arteries to the toes of this foot have a poor capacity for blood flow.

Impairment: 30% impairment of whole man.

Class 4—Impairment of Whole Man, 50-75%.—A patient with vascular disease (or diseases) belongs in this class when any one of the following findings exists: (*a*) intermittent claudication occurring on walking less than 25 yd. or pain at rest occurring at intervals, (*b*) vascular damage as evidenced by physical signs such as amputation at or above the wrist or ankle of one extremity or amputation of two or more digits of two extremities, with evidence of persistent vascular disease, or persistent widespread or deep ulceration involving one extremity, or (*c*) marked edema which cannot be controlled by elastic supports.

Example 1: A 48-year-old man has had recurrent thrombophlebitis in both legs for a number of years. The left leg has been especially affected. A year ago he had to reduce the length of time spent standing in order to lessen the swelling and the pain of a persistent deep ulcer. When he is on his feet he wears heavy elastic stockings, full-length and made to order. Despite these supports there is still extensive edema of the ankles and calves.

Impairment: 50% impairment of the whole man.

Class 5—Impairment of Whole Man, 75-90%.—A patient with vascular disease (or diseases) belongs in this class when any one of the following findings exists: (*a*) severe and constant pain at rest, or (*b*) vascular damage as evidenced by physical signs such as amputation at or above the wrist or ankle of two extremities or amputation of all digits of two or more extremities, with evidence of persistent vascular disease, or persistent widespread or deep ulceration involving two or more extremities.

Note: Edema alone cannot be the basis for classification in class 5.

Example 1: A 54-year-old man was shown to have thromboangiitis obliterans (Buerger's disease) when he lost the great and second toes of the left foot 10 years ago. Bilateral lumbar sympathectomy was performed. He continued to smoke against advice, and two years ago the left leg was amputated 3 in. below the knee. Since then the index and middle fingers of the right hand have been amputated. All sites of amputation healed. There is, however, infection deep in the right foot, and there are signs of severe ischemia nearly to the knee, but further surgery is not deemed necessary at this time.

Impairment: 93% impairment of the whole man; 85% contributed by class 5 peripheral vascular diesase and 52% contributed by amputations (85 combined with 52 is 93).

This classification, without examples, is shown in table 3.

Table 3.—*Classes of Vascular Diseases Affecting the Extremities*

Class 1 (0% Impairment)	Class 2 (5-25% Impairment)	Class 3 (25-50% Impairment)	Class 4 (50-75% Impairment)	Class 5 (75-90% Impairment)
Vascular disease (or diseases) exists	Vascular disease (or diseases) and one or more of the following findings exist	Vascular disease (or diseases) and one or more of the following findings exist	Vascular disease (or diseases) and one or more of the following findings exist	Vascular disease (or diseases) and one or more of the following findings exist
Neither intermittent claudication nor pain at rest is experienced	Intermittent claudication occurring on walking at least 100 yd. at an average pace	Intermittent claudication occurring on walking as little as 25 yd. and no more than 100 yd. at an average pace	Intermittent claudication occurring on walking less than 25 yd. or pain at rest occurring at intervals	Severe and constant pain at rest
	Vascular damage, as evidenced by physical signs such as (*a*) healed painless stump of an amputated single digit, with evidence of persistent vascular disease, or (*b*) healed ulcer	Vascular damage, as evidenced by physical signs such as (*a*) healed amputation of two or more digits of one extremity, with evidence of persistent vascular disease, or (*b*) persistent superficial ulceration	Vascular damage, as evidenced by physical signs such as (*a*) amputation at or above the wrist or ankle of one extremity or amputation of two or more digits of two extremities, with evidence of persistent vascular disease, or (*b*) persistent widespread or deep ulceration involving one extremity	Vascular damage, as evidenced by physical signs such as (*a*) amputation at or above the wrist or ankle of two extremities or amputation of all digits of two or more extremities, with evidence of persistent vascular disease, or (*b*) persistent widespread or deep ulceration involving two or more extremities
Only transient edema is experienced	Persistent edema of a moderate degree incompletely controlled by elastic supports	Marked edema, which is only partially controlled by elastic supports	Marked edema which cannot be controlled by elastic supports	Edema alone cannot be the basis for classification in this class

COMBINED VALUES TABLE

These combined values are based on the formula $A\% + B\%\,(100\% - A\%)$ =combined value of A% and B%. *The guides to the table* are percentages ranging from 1 to 100 printed down the side of the page and across the bottom. To combine any two values, locate the larger of the two on the side of the page and read along that row until you come to the column indicated by the second value at the bottom of the page. At the intersection of this row and column is printed the combined value. For example, to combine 35% and 20% read down the side of the page until you come to the larger value, 35%. Then read across the row you have located until you come to the column indicated by 20% at the bottom of the page. At the intersection of this row and column is the number 48. We say that 35% and 20% combine to 48%. Due to the construction of this table, the larger value must be read at the side of the page.

If three or more values are to be combined, select any two and find their combined value as above. Take this combined value and the third value and find their combined value. This process can be repeated indefinitely, with the value obtained in each case being the combination of all the previous values.

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32	33	33	34	35	35	36	37	37	38	39	39	40	41	42	42	43	44	44	45	46	46	47	48	48	49	50	50	51	52	52	53	54																	
33	34	34	35	36	36	37	38	38	39	40	40	41	42	42	43	44	44	45	46	46	47	48	48	49	50	50	51	52	52	53	54	54	55																
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35	36	36	37	38	38	39	40	40	41	42	42	43	43	44	45	45	46	47	47	48	49	49	50	51	51	52	53	53	54	55	55	56	56	57	58														
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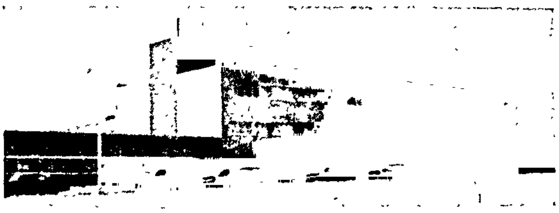
TABLE 4.—*Schedule of Amputations*

Upper Extremity, Type	Impairment of Whole Man, %
Forequarter amputation	70
Disarticulation at shoulder joint	60
Amputation of arm above deltoid insertion	60
Amputation of arm between deltoid insertion and elbow joint	57
Disarticulation at elbow joint	57
Amputation of forearm below elbow joint proximal to insertion of biceps tendon	57
Amputation of forearm below elbow joint distal to insertion of biceps tendon	54
Disarticulation at wrist joint	54
Midcarpal or midmetacarpal amputation of hand	54
Amputation of all fingers except thumb at metacarpophalangeal joints	32
Amputation of thumb	
At metacarpophalangeal joint or with resection of carpometacarpal bone	22
At interphalangeal joint	16
Amputation of index finger	
At metacarpophalangeal joint or with resection of metacarpal bone	14
At proximal interphalangeal joint	11
At distal interphalangeal joint	6
Amputation of middle finger	
At metacarpophalangeal joint or with resection of metacarpal bone	11
At proximal interphalangeal joint	8
At distal interphalangeal joint	5
Amputation of ring finger	
At metacarpophalangeal joint or with resection of metacarpal bone	5
At proximal interphalangeal joint	4
At distal interphalangeal joint	3
Amputation of little finger	
At metacarpophalangeal joint or with resection of metacarpal bone	3
At proximal interphalangeal joint	2
At distal interphalangeal joint	1
Lower Extremity, Type	
Hemipelvectomy	50
Disarticulation at hip joint	40
Amputation above knee joint with short thigh stump (3 in. or less below tuberosity of ischium)	40
Amputation above knee joint with functional stump	36
Disarticulation at knee joint	36
Gritti-Stokes amputation	36
Amputation below knee joint with short stump (3 in. or less below intercondylar notch)	36
Amputation below knee joint with functional stump	28
Amputation at ankle (Syme's)	28
Partial amputation of foot (Chopart's)	21
Midmetatarsal amputation	14
Amputation of all toes	
At metatarsophalangeal joints	8
Amputation of great toe	
With resection of metatarsal bone	8
At metatarsophalangeal joint	5
At interphalangeal joint	4
Amputation of lesser toe (2nd to 5th)	
With resection of metatarsal bone	2
At metatarsophalangeal joint	1
At proximal interphalangeal joint	0
At distal interphalangeal joint	0

GOVERNMENT SERVICES

AIR FORCE

New Hospital.—The USAF Hospital at Tinker Air Force Base, Oklahoma, was formally dedicated in January. This hospital has 75 beds for general medical and surgical inpatients and a comprehensive outpatient service. The 11 acres on which it stands was donated by the Oklahoma City Chamber of Commerce. Lt. Col. Herbert T. Clough Jr. is in command.



Personal.—Colonel Don S. Wenger was named chief professional consultant to the surgeon general. Prior to this appointment Colonel Wenger served as deputy commander and chief of the department of surgery at the U. S. A. F. Hospital, Lackland Air Force Base, Texas.

NAVY

Retirements.—The following medical officers were placed on the retired list: Capt. Ralph K. Hoch after more than 29 years service. His last assignment was as a permanent member of the physical evaluation board, Potomac River Naval Command. ——Capt. Hugh V. O'Connell after more than 21 years service. At the time of his retirement he was assigned at the U. S. Naval Hospital, Oakland, Calif.——Capt. Edward H. Taylor after more than 17 years service. His last assignment was at the Naval Air Station, North Island, San Diego, Calif. ——Capt. Harry G. Beck was retired after 18 years' service by reasons of temporary disability. His last assignment was at the U. S. Naval Shipyard, San Francisco.——Capt. Jarold E. List was retired after 20 years' service. His last assignment was at the Naval Air Station, Memphis, Tenn.——Capt. Walter H. Schwartz was retired after more than 29 years' service. His last assignment was as commanding officer of the U. S. Naval Hospital, Portsmouth, Va.

VETERANS ADMINISTRATION

Personal.—Dr. Oscar Auerbach of the East Orange, N. J., Veterans Administration Hospital and Dr. Ludwik Gross of the Bronx, N. Y., VA hospital were named as senior medical investigators; as such they will engage in full-time medical research. Only four such investigators have been named since the position was created in January, 1959.

PUBLIC HEALTH SERVICE

Fewer Patients in Mental Hospitals.—Again in 1959, for the fourth consecutive year, there was a drop in the number of inpatients in public mental hospitals in the United States. At the end of 1959 there were 542,721 patients in 277 such hospitals or 2,142 fewer than at the end of 1958. While the decline each year was slight, it reversed a decided upward trend that had prevailed until 1956. Between 1903 and 1951, the public mental hospital population quadrupled while the general population only doubled. Commenting on the current trend Dr. Robert H. Felix, director of the National Institute of Mental Health, said that so many factors were involved in these figures that it is unsafe to draw specific conclusions from them, but they undoubtedly reflect a prevailing improvement in the care and treatment of the mentally ill both in and out of mental hospitals.

Dr. Felix attributed this improvement, in part, to a basic change in the philosophy governing mental hospital administration and treatment in the past few years and in the public attitude toward mental illness. No longer is the hospital viewed as a custodial institution. It should function like other hospitals to rehabilitate the patient so that he can return to community living. Dr. Felix also credited new and improved treatment methods, including the wide use of psychoactive drugs, to the increased use of psychiatric beds in general hospitals, and to outpatient psychiatric clinics and other community facilities such as nursing homes, half-way houses, and sheltered workshops. He noted that 20 years ago, only 48 general hospitals treated psychiatric patients. Today there are about 500 such hospitals with psychiatric units and many others that accept mentally ill persons for short-term treatment. About 1,400 outpatient clinics offer psychiatric service.

Influenza Research.—Increased support for influenza research to permit investigators to take advantage of the study opportunities afforded by current influenza outbreaks was announced by the surgeon general. Methods to stimulate such research and to encourage long-range research in influenza and related diseases were developed in January when Dr. Burney called together the service's committee of investigators which is composed of some of the nation's leading authorities on influenza and related diseases. The meeting was held at the National Institutes of Health. Members of the committee agreed to accelerate their own research during this influenza season and to encourage other investigators to conduct influenza studies. The types of problems cited by the committee as needing study are: (1) assessment of the value of the vaccine given in the 1957 epidemic, (2) the present degree of immunity of unvaccinated persons who had influenza in the 1957 epidemic, (3) the physiological effects of influenza on the cardiovascular and respiratory systems, and (4) the neuromuscular effects of influenza.

Members of the committee of investigators are Drs. Robert Wagner, University of Pennsylvania, chairman; George Burch, Tulane University; Fred M. Davenport and Thomas Francis, University of Michigan; Ivan Bennett, Johns Hopkins University; George Hirst, Public Health Research Institute of the City of New York, Inc.; Maxwell Finland, Boston City Hospital; and Roderick Murray, National Institutes of Health.

Training in Microbiology.—The National Institutes of Health has established a new graduate training program in microbiology. A Microbiology Training Committee was appointed by the surgeon general and it held its first meeting at the National Institutes of Health in January. Under the chairmanship of Dr. Morris F. Shaffer, chairman, department of microbiology, Tulane University School of Medicine, the committee will review training grant applications in microbiology and related fields. It will function under Dr. G. Halsey Hunt, chief of the division of general medical sciences, and Dr. Frederick L. Stone, assistant division chief and chief of the research training branch.

This program is designed to support training at predoctoral and postdoctoral levels in medical schools, schools of public health, veterinary schools, other recognized graduate schools, and research institutions in the basic aspects of microbiology, bacteriology, and virology. Microbial genetics, cellular physiology, and cellular metabolism will also be included. The program seeks to provide a basis for the development of senior members of departments in various fields of academic medicine who will teach or perform research work in health-oriented fields. Members of the committee include Drs. George W. Kidder, of Amherst College, Amherst, Mass.; Charles L. Wisseman Jr., of the University of Maryland, Baltimore; Orville Wyss, of the University of Texas, Austin, Texas; Alan W. Bernheimer, of New York University College of Medicine, New York City; S. Edward Sulkin, of the University of Texas, Southwestern Medical School, Dallas, Texas; Ralph Emerson, of the University of California, Berkeley, Calif.; A. F. Rasmussen Jr., of the University of California Medical Center, Los Angeles; and P. W. Wilson, of the University of Wisconsin, College of Agriculture, Madison, Wis.

MEDICAL NEWS

CALIFORNIA

Dr. Pressman Receives Award for Research.—The International Committee for the Gould Award announced the selection of the recipient for 1959—Dr. Joel J. Pressman, University of California at Los Angeles—for his anatomic and radioisotope studies of laryngeal compartments. The Gould Award is presented annually for basic research in laryngology to encourage and reward fundamental investigations in this field. The International Committee for the Gould Award for the year 1960 includes: Sir Victor Negus, London, England; Dr. Cotoji Satta, Tokyo, Japan; Prof. Dr. Luzius Ruedi, Zurich, Switzerland; and Dr. Hans V. Von Leden, medical director, The William and Harriet Gould Foundation, 30 N. Michigan Ave., Chicago 2. The Gould Award consists of a plaque and an honorarium of $300.

Plan Hospital in La Jolla.—Plans for a new Scripps Memorial Hospital in La Jolla, construction of which is estimated to cost 4 million dollars, are being prepared. According to Mr. Fred W. Trader, hospital administrator, construction of the seven-story, 250-bed facility is expected to start in the fall of this year and will be completed about 18 months later. Plans call for 40 beds in the maternity section, with the remaining 210 allocated to medical and surgical cases. There will also be pediatrics, x-ray section, clinical laboratory, physical medicine, and dietary facilities. The seven-story nursing unit will be serviced by a free-standing elevator tower. The hospital will have a central nursing station to care for patients in rooms arranged around the perimeter of the building. All surgical, adjunct, and administration facilities are located on the ground level. Service facilities are grouped in the lower level, with the central medical supply for the entire building located under the elevator wing. Located on a 40-acre site on Torrey Pines Mesa, the hospital's patient rooms will have cantilevered balconies in the main tower. The hospital is designed for future expansion with the addition of another nursing unit on the opposite side of the elevator tower.

COLORADO

Dr. Longmire Gives Annual Lecture.—Dr. William P. Longmire Jr., head, department of surgery, University of California at Los Angeles School of Medicine, delivered the annual Clagett Lecture at t University of Colorado Medical Center, Denve March 2. He presented "Current Surgical Probler in the Treatment of Angina Pectoris." The lectu is sponsored by the C. U. department of surger and was endowed by Dr. Oscar T. Clagett, Ma Clinic surgeon, in memory of his father, the la Dr. O. F. Clagett, who was in practice for ma years at Rifle, Colo.

KENTUCKY

Program for Postgraduate Education.—The Ke tucky State Medical Association is working clos with the University of Louisville and the Univ sity of Kentucky Medical Schools in sponsoring active program of postgraduate education. It appropriated $10,000 for this purpose. Friedri Hertle, Ph.D., a native of Germany, has been e ployed as full-time director of the program. Hertle received his Ph.D. in economics and bu ness administration from the University of Bas He came to the United States in 1956. The Univ sity of Louisville has provided a furnished office a building directly across the street from the me cal school, formerly housing the School of Ph macy of the University of Kentucky, which moved to the Lexington campus. The U. of L. leased the building from the U. of K., and locati the postgraduate headquarters in that buildi "serve to emphasize the cooperative nature of program." Dr. Hertle will work under the directi of the state association's committee on postgradu education, headed by Dr. Walter S. Coe, Louisvil

LOUISIANA

Medical Assembly in New Orleans.—The 23 annual meeting of the New Orleans Graduate Me cal Assembly will be held March 7-10 at The Roo velt Hotel, New Orleans. Twenty-one guest spe ers will participate in the program and present talks. A clinical pathological conference is sche uled for March 7, 8:30 p. m. Round-table luncheo are scheduled for specialty groups March 8 and and for the general assembly, March 9. A panel d cussion, "The Recognition and Management Metabolic Alterations Resulting from Trauma," w be held March 9, 8:30 p. m. Films covering rece advances and semantic considerations in surge medicine, and allied specialties will be shown dai Technical exhibits are planned. The program is a ceptable for 28 hours category I credit by t American Academy of General Practice. The reg tration fee of $20 covers all aspects of the assemb

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

For information, write Miss Irma B. Sherwood, 1430 Tulane Ave., New Orleans 12, Executive Secretary.

MASSACHUSETTS

British Zoologist to Lecture.—Dr. Peter B. Medawar, Jodrell Professor of Zoology at the University College, University of London, will deliver the annual Dunham Lectures at the Harvard Medical School, Boston, on March 21, 23, and 25. His general topic for the three lectures will be "The Immunology of Transplantation." The lectures will be given at 5 p. m. each day in Amphitheatre D at the medical school. Dr. Bernard D. Davis, professor of bacteriology and immunology at Harvard and chairman of the Dunham Lecture Committee, will preside.

Plan Expansion of Nutrition Research Facilities.—A gift of $100,000 a year for 10 years from General Foods Corporation will provide for expansion of the nutritional research laboratories of the Harvard School of Public Health. President Nathan M. Pusey of Harvard, announcing the General Foods gift for construction of the laboratory unit, said it is the largest gift ever made by any business corporation for the capital purposes of Harvard University. The new four-story nutrition laboratory will be part of a projected research structure for the School of Public Health in Boston. The nutrition laboratory will occupy the top of an 11-story research building of the Harvard School of Public Health (with two research floors below ground) to be started this spring. Four additional floors will be added later. The 11-story structure will be financed in part by a grant of $1,450,000 from the National Institutes of Health (U. S. Department of Health, Education and Welfare) through its Health Research Facilities Branch, and in part by gifts of individuals, corporations, and foundations.

MICHIGAN

Research Forum for Students.—Twelve undergraduate medical students presented formal papers on their own medical research in the University of Michigan Medical School, Ann Arbor, on Feb. 16. The 12 were selected for the annual Student Research Forum sponsored by the medical students' honorary society, Alpha Omega Alpha. The program was held in University Hospital. Dr. William N. Hubbard, dean of the Medical School, opened the forum with an address. Dr. John W. Henderson, associate professor of ophthalmology, and Keith S. Henley, M.B., assistant professor of internal medicine, presided over the formal presentations.

Report on Rabies.—Confirmed rabies cases in skunks numbered an all-time high of 19 in Michigan during 1959, the state health department announced. Previous high for skunk rabies cases was 10, reported in both 1958 and 1957. Rabies cases from all types of animals totaled 52 in Michigan last year. This was the highest total since 117 cases were reported in 1954. Contributing to last year's 52 cases were 20 dogs, 5 cats, 4 cows, 2 foxes, 1 horse, and 1 bat. Six counties in central Michigan accounted for 13 of the 19 skunk cases. Last year rabid skunks are known to have attacked two humans, 29 dogs, and 6 cats in Michigan. The two persons bitten by the skunks received antirabies treatment and neither contracted rabies. Michigan also recorded 30 other human exposures to rabies last year, 20 of them from dogs, but these persons also were treated and none died. It was the 11th straight year in which Michigan was free from human rabies deaths.

Nutrition Conference in Detroit.—The sixth annual nutrition conference sponsored by Wayne State University College of Medicine will be held Friday, March 18, 1960. Speakers on the general subject "Prospects in Nutrition" will include Drs. Paul L. Day, Ph.D., of the U. S. Food and Drug Administration; Howard A. Schneider of the Rockefeller Institute; Philip L. White, Sc.D., of the American Medical Association; and James L. Wilson, of the University of Michigan. Members of the American Medical Association are invited. For information, write Mr. James M. Orten, chairman, Publicity Committee, Wayne State University, 1401 Rivard St., Detroit 7.

Nobel Prize Winners to Lecture.—British and American Nobel Prize winners are among the 13 biological scientists who are listed as speakers in a public lecture series sponsored by the Institute of Science and Technology at the University of Michigan. Sir Hans Krebs, of Oxford University, and Dr. Arthur Kornberg, of Stanford, won Nobel Prizes in physiology and medicine in 1953 and 1959, respectively. Sir Hans will lecture March 8, and Dr. Kornberg April 8, in the series titled "The Molecular Control of Cellular Activity." The series is focused on areas of biology basic to understanding how living organisms may be affected by space phenomena. Such studies have since last year been referred to as "exobiology." The studies are also referred to as "space biology." Dr. Paul A. Weiss, of the Rockefeller Institute, opened the series March 1, presenting "From Cell to Molecule." Each lecture will be at 4 p. m. in the third level amphitheater, Medical Science Building, admission-free and open to the public. Hewson H. Swift, Ph.D., of the University of Chicago, spoke March 3, and Dr. Torbjorn Caspersson, director of the Karolinska Institute, Stockholm, Sweden, spoke March 4. The series will continue through April.

Grant to Aid Research Project.—The University of Michigan announced that General Motors Corporation will donate half a million dollars to the university over the next five years for research into industrial health and the peaceful uses of atomic energy. Terms of the grant provide $350,000 for the Institute of Industrial Health which was created in 1950 when GM donated 1.5 million dollars to the university's Memorial–Phoenix Project for atomic research. The Institute of Industrial Health does research in the prevention, diagnosis, and treatment of occupational diseases. Results are available to American industry. The Phoenix project is the university's memorial to its dead in World War II. It is devoted to the peaceful uses of atomic energy and has received 8 million dollars in gifts since its creation. The university is conducting a drive to raise 2 million dollars for the Phoenix Project and has accumulated $760,000, including the General Motors gift.

NEW YORK

Dr. Handy Receives Cancer Medal.—The New York State Division of the American Cancer Society recently awarded a gold medal to Dr. Vincent H. Handy, assistant director of the Bureau of Cancer Control, New York State Health Department. The award was given to Dr. Handy in recognition of his "distinguished service in the field of cancer control." Dr. Handy is chairman of the professional information committee of the New York State division.

New York City

Faculty Appointments.—Four faculty members were appointed at the State University of New York Downstate Medical Center in Brooklyn. Dr. David L. Benninghoff, formerly instructor in radiology at Temple University Medical School, Philadelphia, was named assistant professor of radiology. Named assistant professor of environmental medicine and community health was Dr. David Hewitt, of Oxford, England. Dr. Daniel S. Feldman, director of the neurological division of Maimonides Hospital, Brooklyn, was named assistant professor of neurology. The final appointment went to Dr. Norman S. Blackman, cardiac consultant to the New York City Department of Health, who was named clinical assistant professor of medicine.

Program for Training in Orthotics.—New York University's School of Education will offer, beginning next fall, a four-year undergraduate curriculum in prosthetics and orthotics—the design, fabrication, and fitting of artificial limbs and braces. The program, developed in conjunction with the university's postgraduate medical school and college of engineering, is intended primarily for persons interested in the clinical practice of prosthetics and orthotics. The curriculum includes courses in English and speech; mathematics; the physical, biological, and chemical sciences; basic engineering; psychology; sociology and social studies; and shop methods. Students in the program, who will number no more than 15 each year, also will take specialized professional courses in upper and lower extremity prosthetics and orthotics, as well as in orthotics for the trunk. These will be supplemented by a clinical training program developed in cooperation with the American Orthotic and Prosthetic Association and a number of certified limb- and brace-making facilities throughout the country. Information may be obtained by writing Sidney Fishman, Ph.D., Prosthetics Education, New York University, 342 E. 26th St., New York 10.

PENNSYLVANIA

Forum on Radiation Effects.—Woman's Medical College of Pennsylvania, Philadelphia, has scheduled its annual forum celebrating Founders' Day for Wednesday, March 9, from 3 to 9 p. m. The subject, "Atoms, Rays and People—a Symposium on the Physiological Effects of Ionizing Radiation," was announced by Dr. Irwin J. Pincus, associate professor of medicine. The afternoon session, on the technical aspects of the subject, will be moderated by Dr. Harriet Hardy, assistant medical director, Massachusetts Institute of Technology. It will be held in the college auditorium at 3 p. m. The topics and speakers will be as follows:

Use of Isotopes in Medicine, Dr. Harvey D. Bruner, chief, medical research branch, Atomic Energy Commission.
Delayed Illness Resulting from Large Amounts of Ionizing Radiation, Robert A. Dudley, Ph.D., department of physics, M. I. T.
Biological Hazards of Ionizing Radiation, Max Zelle, Ph.D., chief, biology branch, Atomic Energy Commission.
The Establishment of a Health Physics Program, Elda Anderson, Ph.D., chief, health and training section, Oak Ridge National Laboratories.

The evening session at 8 p. m. is especially planned for the layman and will be held in the auditorium of the Eastern Pennsylvania Psychiatric Institute, adjacent to the college. Dr. Pincus will be the moderator and the speakers will be: W. H. Langham, Ph.D., biomedical research group leader, Los Alamos Scientific Laboratories, "Present Status of the World-Wide Fallout Problem," and Dr. Charles W. Shilling, deputy director, division of biology, Atomic Energy Commission, "The Effects of Radiation on the World's Most Precious Material." For information, write Dr. Pincus, Woman's Medical College of Pennsylvania, 3300 Henry Ave., Philadelphia 29.

TEXAS

Clinical Conference in Dallas.—The 29th annual spring clinical conference of the Dallas Southern Clinical Society will be held March 21-23 at the Statler Hilton Hotel, Dallas. The program includes the following guest speakers:

Drs. Douglas N. Buchman, Chicago; Edward L. Compere, Chicago; Robert E. Cooke, Baltimore; George Crile Jr., Cleveland; Arthur G. DeVoe, New York City; William Dock, Brooklyn; James E. Eckenhoff, Philadelphia; Herman Elwyn, New York City; Benjamin Felson, Cincinnati; Aram Glorig Jr., Los Angeles; Milton Helpern, New York City; Frank Hinman Jr., San Francisco; S. Leon Israel, Philadelphia; Charles G. Johnston, Detroit; Lawrence S. Kubie, New York City; Daniel G. Morton, Los Angeles; Robert E. Votaw, St. Louis; William M. M. Kirby, Seattle.

Round-table luncheons will consider medical, surgical, EENT, orthopedic, urological, pediatric, and obstetrics-gynecology problems. Postgraduate lectures, panel discussions, a clinical pathological conference, and technical exhibits are planned. The social program includes a dinner dance.

VERMONT

Drs. Raab and Pierce to Retire.—Dr. Wilhelm Raab will retire as professor and chairman, division of experimental medicine, University of Vermont College of Medicine, Burlington, effective June 30. Dr. Raab was born in Vienna, Austria. He received M.D. degrees from the University of Vienna and from the German University of Prague. He was appointed to the College of Medicine faculty in 1939 as associate professor. Harold B. Pierce, Ph.D., will retire as professor and chairman, department of biochemistry, effective June 30. Dr. Pierce received his Ph.D. from the University of Rochester, N. Y. He was appointed to the faculty in 1937 as associate professor.

WISCONSIN

Annual Lecture.—Dr. Thomas M. DuRant, professor of medicine, Temple University Medical Center, Philadelphia, will be the speaker at the annual Malcolm F. Rogers lecture sponsored by the Wisconsin Heart Association in cooperation with the University of Wisconsin School of Medicine on March 14. Dr. DuRant will present "Bedside Management of Cardiac Arrhythmias" at 8 p. m. in the medical school's Bardeen Auditorium in Madison.

GENERAL

Change Dates for Meeting of Maxillofacial Surgeons.—Dr. Edward C. Hinds, Secretary, American Society of Maxillofacial Surgeons, P. O. Box 20068, Houston 25, Texas, announced that because of a conflict with the meeting of the American Association of Plastic Surgeons, the meeting dates of the American Society of Maxillofacial Surgeons has been changed from May 15-18, 1960, to March 27-31, 1960.

Laryngologists Meeting in Florida.—The American Laryngological Association will meet at the Deauville Hotel, Miami Beach, Fla., March 18-19. Dr. William J. McNally, Montreal, Canada, president of the association, will open the meeting with an address. The program includes 18 scientific papers, and the following papers will include foreign authors:

Phonation: Clinical Testing versus Electromyography, Dr. David W. Brewer, Syracuse, N. Y., and Dr. K. Faa borg-Andersen, Falstar, Denmark.

The Sphenoidal Sinus in Its Relation to the Sellar Turcica, Dr. Gunnar Hammer, Goteborg, Sweden.

Trans-antro Sphenoidal Hypophysectomy, Dr. Carle-Axel Hamberger, Goteborg, Sweden.

Early Invasion of the Thyroid Gland in Carcinoma of the Larynx, Dr. Ricardo Tapia Aouna, Mexico.

For information, write Dr. Lyman G. Richards, Massachusetts Institute of Technology, Cambridge 39, Mass.

Triological Meeting in Miami Beach.—The 63rd annual meeting of the American Laryngological, Rhinological and Otological Society, Inc., the "Triological Society," will be held March 15-17 at the Deauville Hotel, Miami Beach, Fla. Following a business meeting the morning of March 15, Dr. Theodore E. Walsh, St. Louis, president of the society, will speak. Mr. Terence Cawthorne, London, England, guest of honor at the meeting, will present "The Influence of Deafness on the Creative Instincts." A panel discussion, "Tympanoplasty," will be moderated by Dr. Albert C. Furstenberg, Ann Arbor, Mich., and participants will include Dr. Harold F. Schuknecht, Detroit; Dr. Joseph E. Sullivan, Toronto, Canada; and Dr. Nils Richtner, Stockholm, Sweden. The following papers include invited authors:

Dysmetria in Post-Caloric Nystagmus: Its Clinical Significance, *Drs. Malcolm H. Stroud, St. Louis, and J. Santiago Riesco, Santiago, Chile.*

Aural Cholesteatoma: Experimental Observations, Drs. John R. Lindsay, and Caesar Fernandez, Chicago.

Tonsillectomy for Acute Peritonsillar Abcess, Drs. Benjamin M. Volk and Edward C. Brandow Jr., Albany, N. Y.

Method for the Identification and Localization of Cerebrospinal Fluid Rhinorrhea and Otorrhea, Drs. G. O'Neil Proud and Fernando R. Kirchner, Kansas City, Kan.

Isolated Keratosis of the Larynx: Its Relation to Carcinoma, Drs. Malcolm H. McGavran and Walter C. Bauer, St. Louis.

The Procurement and Processing of Endoscopic Biopsies, Drs. Paul H. Holinger, Kenneth C. Johnston, and Edwin F. Hirsch, Chicago.

A social program is planned. For information, write Dr. C. Stewart Nash, 708 Medical Arts Building, Rochester 7, N. Y., Secretary.

Appointments to Pharmaceutical Association.—Two appointments to the staff of the Pharmaceutical Manufacturers Association were announced Feb. 9 by Dr. Austin Smith, president. They are Dr. Robert J. Benford, former editor of the *U. S. Armed Forces Medical Journal* of Washington, D. C., to be director of medical relations for PMA; and Mr. Milton Golin, former editor of the "Medicine at Work" section of THE JOURNAL, to be assistant to the president of PMA for special projects. Both men have assumed their new duties.

Russian Scientists Tour U. S.—Four touring Soviet radiobiologists arrived in the U. S. in mid-December under the new U. S.-U. S. S. R. scientific and cultural exchange program and toured New York, Washington, D. C., Baltimore, Chicago, San Francisco, Los Angeles, and Portland, Ore. They were repaying a visit to Russia in October and November by a six-man American delegation. The Russian visitors were Dr. Mikhail Pobedinski, chairman of the group and director of the Central Scientific Research Institute for Roentgenology, Radiology, and Cancer in Leningrad; Dr. Georgie A. Zedgenidze, who occupies the chair of roentgenology at the Academy of Medical Sciences in Leningrad; Dr. Alexander Pavlov, lecturer on radiation medicine, roentgenology, and radiology at the Moscow Stomatology Institute; and Dr. Valerie Bochkarev, department chief of the Institute of Biophysics and Radiation Medicine at the U. S. S. R. Ministry of Health in Moscow.

Maxillofacial Surgeons Meeting in Los Angeles.—The annual meeting of the American Society of Maxillofacial Surgeons will be held at the Ambassador Hotel, Los Angeles, March 27-31. All members of the medical profession are invited. The program includes scientific and clinical sessions, and subjects will include the following: growth of jaws in relation to various deformities, diseases of the tongue and their treatment, and trauma of the face. A panel discussion, "Cleft Palate and Cleft Lip," is planned. A general discussion, "Geriatrics in Head and Neck Problems," is scheduled. Scientific exhibits have been arranged. The social program includes two dinners, at the first of which (March 28) Dr. Truman G. Blocker Jr., Galveston, Tex., will be presented the distinguished service award of the society. At the second dinner (March 30) officers will be elected and Dr. Casper M. Epsteen, Chicago, will give the presidential address. For information, write Dr. Edward C. Hinds, 1508 Medical Towers, Houston 25, Texas, Secretary.

Health Forum in Miami Beach.—New guidelines for programs to promote the health of older people are the goal of the 1960 National Health Forum at the Carillon Hotel, Miami Beach, Fla., March 14-17. Taking part in the sessions, sponsored by the National Health Council, will be invited authorities representing health and medicine, education, religion, government, social welfare, industry, and labor. They will discuss reports on current and contemplated research on the aging and exchange information on programs for the aging under way in this country and abroad. Chairman of the forum is Dr. Edward L. Bortz, of Philadelphia, president-elect of the American Geriatrics Society and a former president of the American Medical Association. Principal speakers at the 1960 forum will include Dr. Ali Berggren, governmental supervisor, Royal Board of Social Welfare, Stockholm, Sweden; Dr. Leroy E. Burney, Surgeon General, U. S. Public Health Service; G. Warfield Hobbs, New York City banker and chairman, National Committee on the Aging, National Social Welfare Assembly; and Francis H. Horn, Ph.D., president, University of Rhode Island. Group discussions are scheduled on problems which the increasing proportion of older people in the population pose for employers and workers, health care professions, public health, and public welfare. Other groups will discuss services for the aged at home, and psychiatry's role in healthy aging. The National Health Council will hold its annual meeting in conjunction with the forum. Member organizations of the council include 70 national health, professional, government, and other organizations with interests related to promotion of health. Headquarters of the council are at 1790 Broadway, New York 19. Philip E. Ryan is executive director.

CORRECTIONS

Seymour Blau.—In the item entitled "Counterfeiters of Tranquilizer Drugs Sentenced" in The Journal, Nov. 21, 1959, page 1709, one Seymour Blau was said to have pleaded guilty to five counts and testified for the government against Spandau. Dr. Seymour H. Blau of Jersey City, N. J. has requested The Journal to publish a statement that he has no connection whatsoever with the Seymour Blau mentioned in the item referred to above.

Sulfonamide Preparation C 17922 (Orisul): Clinical and Experimental Study of Its Use in Genitourinary Infections: Preliminary Report.—In the abstract entitled The Sulfonamide Preparation C 17922 (Orisul): Clinical and Experimental Study of Its Use in Genitourinary Infections: Preliminary Report, which appeared in The Journal, Dec. 19, 1959, page 2267, the dosage all through the abstract should have been in grams and not in milligrams.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. March 16, 1960 and Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities. June 21-22 and Sept. 7-8. Part II, Various Cities, April 26-27. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

Alabama: *Examination.* Montgomery, June 21-23. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

Alaska:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

Arkansas:* *Examination and Reciprocity.* Little Rock, June 9-10 Sec., Dr. Joe Verser, Harrisburg.

California: *Written.* Los Angeles, March 7-10; San Francisco, June 20-23; Los Angeles, Aug. 22-25 and Sacramento, Oct. 17-20. *Oral and Clinical.* Los Angeles, March 6; San Francisco, June 19; Los Angeles, Aug. 21, and Los Angeles, Nov. 29. *Oral for Reciprocity Applicants.* Los Angeles, Mar. 5; San Francisco, June 18; Los Angeles, Aug. 20 and Nov. 19. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

Canal Zone: On Application. Acting Sec., Dr. B. K. Levin, Health Bureau, Balboa Heights.

Colorado:* *Reciprocity.* Denver, April 12. *Examination.* Denver, June 14-15. Sec., Dr. John B. Farley, 1612 Tremont Place, Denver 2.

Connecticut:* *Regular. Examination.* Hartford, Mar. 8-10. Sec., Dr. Stanley B. Weld, 160 St. Ronan St., New Haven. *Homeopathic. Examination.* Derby, Mar. 8. Sec., Dr. Ronald A. Davis, 38 Elizabeth St., Dover.

Delaware: *Examination and Endorsement.* Dover, June 12-14 and July 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

District of Columbia:* *Reciprocity.* Washington, March 14. *Examination.* Washington, June 13-14. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., N.W., Washington 6.

Florida:* *Examination.* Miami Beach, June 19-21. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

Georgia: *Examination and Reciprocity.* Atlanta, June. Sec., Mr. Cecil L. Clifton, 224 State Capitol, Atlanta 3.

Guam: *Subject to Call.* Act Sec., Dr. F. L. Conklin, Agana.

daho: *Examination and Endorsement.* Boise, July 11-13. Exec. Sec., Mr. Armand L. Bird, 304 Sonna Bldg., Boise.

ndiana: *Examination.* Indianapolis, June 22-24. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

Maine: *Examination and Reciprocity.* Brunswick, March 8-10. Sec., Dr. Daniel F. Hanley, Box 637, Brunswick.

Maryland: *Examination.* Baltimore, June 15-18. Sec., Dr. Frank K. Morris, 1215 Cathedral St., Baltimore 1.

Michigan:* *Examination.* Ann Arbor and Detroit, June 6-8. Sec., Dr. E. C. Swanson, 118 Stevens T Mason Bldg., Lansing.

Mississippi: *Examination.* Jackson, June. Sec., Dr. A. L. Gray, Old Capitol, Jackson 13.

Montana: *Examination and Reciprocity.* Helena, April 5. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

Nebraska:* *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada:* *Examination and Reciprocity and Endorsement.* Reno, March 8. Sec., Dr. G. H. Ross, 112 No. Cury St., Carson City.

New Hampshire: *Examination.* Concord. March 9-12. Sec., Dr. Edward W. Colby, 61 South Spring St., Concord.

New Mexico:* *Examination and Reciprocity.* Santa Fe, May 16-17. Sec., Dr. R. C. Derbyshire, 227 East Palace Ave., Santa Fe.

New York: *Examination.* Albany, Buffalo, New York City, Rochester and Syracuse, June 28-July 1. Sec., Dr. Stiles D. Ezell, 23 S. Pearl Street, Albany.

North Carolina: *Endorsement.* Raleigh, May 9. *Examination and Endorsement.* Raleigh, June 20-23. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

North Dakota: *Examination and Reciprocity.* Grand Forks, July 6-9. Sec., Dr. C. J. Glaspel, Grafton.

Ohio: *Reciprocity.* Columbus, April 5 and June 17. *Examination.* Columbus, June 16-18. Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

Oklahoma:* *Examination and Endorsement.* Oklahoma City, May 31-June 1. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

Oregon:* *Reciprocity and Endorsement.* Portland, April 14-16. *Examination.* Portland, July. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

Pennsylvania: *Examination.* Philadelphia and Pittsburgh, July 5-7. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

Rhode Island:* *Endorsement.* Providence, March 24. *Examination.* Providence, April 7-8. Administrator of Professional Regulations, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

Tennessee:* *Examination.* Memphis, March 23-24. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis 3.

Texas:* *Examination and Reciprocity.* Fort Worth, June 20-22. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

Utah: *Examination.* Salt Lake City, July 6-8. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

Virginia: *Examination and Reciprocity.* Richmond, June 13-17. Address: Board of Medical Examiners, 631 First St. S.W., Roanoke.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Arizona: *Examination.* Tucson, March 18. *Endorsement.* Tucson, March 15. Sec., Mr. Herman E. Bateman, University of Arizona, Tucson.

Arkansas: *Examination.* Little Rock, April 21-22. Sec., Dr. A. W. Ford, Department of Education, Education Bldg., Little Rock.

District of Columbia: *Examination.* Washington, May 23-24. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., Washington 6.

Florida: *Examination.* Miami, June 4. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

Iowa: *Examination and Reciprocity.* Des Moines, April 12. Sec., Mr. Elmer W. Hertel, Wartburg College, Waverly.

Kansas: *Examination.* Kansas City, June 10-12. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

Minnesota: *Examination.* Minneapolis, April 5-6. Sec., Dr. Raymond N. Bieter, 165 Millard Hall, University of Minnesota, Minneapolis.

Nebraska: *Examination.* Omaha, May 3-4. Sec., Mr. R. K. Kirkman, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada: *Examination.* Reno, March. Sec., Dr. Kenneth C. Kemp, Box 9355, University of Nevada, Reno.

Oklahoma: *Examination.* Oklahoma City, April 15-16. Exec. Sec., Mrs. E. L. Haidek, 813 Braniff Bldg., Oklahoma City.

Tennessee: *Examination.* Memphis and Nashville, March 23-24. Sec., Dr. O. W. Hyman, 62 S. Dunlap St., Memphis.

Texas: *Examination.* Austin, Houston and Galveston. Sec., Dr. Cornelia M. Smith, State Office Bldg., 201 East 14th St., Austin.

Washington: *Examination.* Seattle, July 13-14. Administrator, Mr. Thomas A. Carter, Department of Licenses, Capitol Bldg., Olympia.

Wisconsin: *Examination.* Madison, April 9. Milwaukee, June 4. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

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*Basic Science Certificate required.

DEATHS

Ackerman, Harry Ⓜ New York City; Long Island College Hospital, Brooklyn, 1915; formerly on the staff of the Bronx Hospital; veteran of World War I; died in the Montefiore Hospital, Dec. 4, aged 73.

Boese, William Henry Ⓜ New York City; Columbia University College of Physicians and Surgeons, New York City, 1904; died Dec. 4, aged 81.

Bradford, Mark Averill, Hendersonville, N. C.; University of Pennsylvania School of Medicine, Philadelphia, 1911; veteran of World War I; fellow of the American College of Surgeons; served on the board of directors of Margaret R. Pardee Memorial Hospital; for many years on the staff of the South Side Hospital in Pittsburgh; died in Asheville Dec. 16, aged 72.

Brown, Wilbur Max Ⓜ Mansfield, Ohio; University of Arkansas School of Medicine, Little Rock, 1935; interned at the Henry Ford Hospital in Detroit, where he served a residency; specialist certified by the American Board of Ophthalmology; fellow of the International College of Surgeons and the American College of Surgeons; veteran of World War II; on the staff of the Mansfield General Hospital; died Dec. 4, aged 51.

Buie, Roderick Mark Sr. Ⓜ Greensboro, N. C.; Jefferson Medical College of Philadelphia, 1914; past-president of the North Carolina Public Health Association; for many years county health officer; served as county physician; past-vice-president of the Guilford County Medical Society; veteran of World War I; associated with the Moses H. Cone Memorial and Wesley Long Community hospitals; died Dec. 1, aged 74.

Butler, Albert Ⓜ Ashland, Wis.; University of Nebraska College of Medicine, Omaha, 1896; veteran of World War I; consultant of the Trinity Lutheran Hospital; died Dec. 2, aged 83.

Clarke, T. Wood Ⓜ Utica, N. Y.; Johns Hopkins University School of Medicine, Baltimore, 1902; specialist certified by the American Board of Pediatrics; past-president of the Oneida County Medical Society and the Utica Academy of Medicine; associated with the Faxton and St. Elizabeth hospitals; author of several books; died Dec. 17, aged 81.

Cook, Ralph Gilmore Ⓜ Kalamazoo, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1905; for many years county coroner; past-president of the Kalamazoo Academy of Medicine; served on the staff of the Fairmont Hospital; died in the Bronson Hospital Dec. 9, aged 78.

Copeland, Paul Richard Ⓜ Beckley, W. Va.; National University of Arts and Sciences Medical Department, St. Louis, 1917; served as manager of the Veterans Administration Hospital; formerly associated with the Veterans Administration Hospital in Huntington and the Veterans Administration Hospital in Martinsburg; died Dec. 12, aged 65.

Dermott, Michael Joseph, Baltimore; University of Maryland School of Medicine, Baltimore, 1910; died Nov. 29, aged 71.

Ehrenreich, Max Milton, New York City; Julius-Maximilians Universität Medizinische Fakultät, Wurzburg, Bavaria, Germany, 1904; for many years physician for the Department of Correction; died Dec. 14, aged 79.

Evans, James Miller Ⓜ New York City; Jefferson Medical College of Philadelphia, 1919; on the staffs of the Hospital for Special Surgery, Misericordia Hospital, and Metropolitan Hospital; consultant at Goldwater Memorial Hospital; formerly on the staff of the Veterans Administration Hospital; died Dec. 11, aged 65.

Gnassi, Carmine P., Hoboken, N. J.; Universita di Napoli Facolta di Medicina e Chirurgia, Italy, 1892; served on the staffs of the Medical Center of Jersey City and the Margaret Hague Maternity Hospital, Jersey City; died Dec. 13, aged 85.

Guten, Seymour David Ⓜ Chicago; Chicago Medical School, 1946; interned at the Edgewater Hospital, where he was on the staff; member of the American Academy of General Practice; died in the Michael Reese Hospital Dec. 14, aged 41.

Hathaway, Clayton Bishop Ⓜ Butler, Ind.; Indiana University School of Medicine, Indianapolis, 1928; served as county coroner; member of the school board; died Nov. 30, aged 59.

Heda, Frank Ⓜ Chicago; Loyola University College of Medicine, Chicago, 1916; member and past-president of the staff of the Roseland Community Hospital; past-president of the Calumet Branch of the Chicago Medical Society; member of the American Academy of General Practice; died Dec. 15, aged 68.

Henry, Clifford Elmore Ⓜ Milwaukee; Jefferson Medical College of Philadelphia, 1896; fellow of

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Ⓜ Indicates Member of the American Medical Association.

the American College of Physicians; veteran of World War I; died in St. Camillus Hospital, Wauwatosa Nov. 19, aged 85.

Hoag, Louis, West Chester, Pa.; Harvard Medical School, Boston, 1903; died Sept. 15, aged 81.

Hoffman, Lloyd Oliver Ⓜ Omaha; University of Nebraska College of Medicine, Omaha, 1919; charter member of the Central Association of Obstetrics and Gynecology; for many years on the faculty of his alma mater; died Dec. 2, aged 62.

Holt, Russell Daniel Ⓜ Meridian, Texas; Tulane University School of Medicine, New Orleans, 1936; member of the American Academy of General Practice and the Aero Medical Association; part-owner and superintendent of the Holt Archer Hospital and Clinic; died in Dallas Dec. 8, aged 49.

Hopper, Walter Owsley Ⓜ Perryville, Ky.; Hospital College of Medicine, Louisville, 1901; past-president of the Central Kentucky Medical Society; member of the American Academy of General Practice; for many years member of the county board of health; veteran of World War I; died in the Ephraim McDowell Memorial Hospital, Danville, Dec. 5, aged 88.

Horrocks, Gilles Edward Ⓜ Colonel, U. S. Army, retired, San Antonio, Texas; Harvard Medical School, Boston, 1927; certified by the National Board of Medical Examiners; died Dec. 12, aged 61.

Hullinghorst, Robert Leonce Ⓜ Colonel, U. S. Army, Washington, D. C.; born Sept. 9, 1916; Louisiana State University School of Medicine, New Orleans, 1939; interned at the Gorgas Hospital in Ancon, Canal Zone; served a residency at the Letterman General Hospital in San Francisco and the Fitzsimons General Hospital in Denver; commissioned in the regular Army in 1939; during World War II served with the 90th Infantry Division and from 1943 to 1945 was with the 34th Medical Battalion, the 32nd and 139th Evacuation hospitals in the European Theater of Operations; for his service during the war, received the Legion of Merit; since 1958 deputy commander of the Army Surgeon General's Medical Research and Development Command; served in the Army Surgeon General's Office since 1956, first as chief of the research and development division, and after the Army medical research and development command was established in August 1958 served as commander pending arrival of a general officer; formerly deputy director of the Walter Reed Army Institute of Research, Walter Reed Army Medical Center; from 1949 to 1952 commanded the 406th Medical General Laboratory in Tokyo; served as deputy director of the communicable disease division at the Army Medical Service Graduate School, Walter Reed Army Medical Center, 1952-1953 and during the next year was chief research division, at the Armed Forces Institute of Pathology, Washington, D. C.; in 1954-1955 was assistant commandant and later deputy commandant at the Army Medical Service Graduate School at Walter Reed Army Medical Center; in 1955 became deputy director of the Walter Reed Army Institute of Research; member of the College of American Pathologists, American Society of Clinical Pathologists, International Academy of Pathology, National Research Council and the New York Academy of Sciences; specialist certified by the American Board of Pathology; died in the Naval Hospital, Bethesda, Dec. 10, aged 43.

Hunter, John Pullen Ⓜ Cary, N. C.; Jefferson Medical College of Philadelphia, 1919; past-president of the Wake County Medical Society; served as a member of the county board of education; veteran of World War I; formerly mayor; died in the Veterans Administration Hospital, Durham, Dec. 1, aged 63.

Imler, Harper George, San Marino, Calif.; University of Pennsylvania School of Medicine, Philadelphia, 1918; veteran of World Wars I and II; died Dec. 8, aged 67.

Jacobs, David Elias Ⓜ Erie, Pa.; Jefferson Medical College of Philadelphia, 1899; died Nov. 29, aged 90.

Johnson, Harry T. Ⓜ Waltham, Mass.; Middlesex College of Medicine, Cambridge, 1930; died in the Waltham Hospital Nov. 4, aged 58.

Kirschbaum, Harry M. Ⓜ Detroit; Detroit College of Medicine and Surgery, 1921; specialist certified by the American Board of Obstetrics and Gynecology; member of the Central Association of Obstetricians and Gynecologists and the Aero Medical Association; fellow of the International College of Surgeons and the American College of Surgeons; veteran of World Wars I and II; associated with the Woman's and Sinai hospitals; died Dec. 2, aged 59.

Kohlmoos, Henry J. Oakland, Calif.; Hessische Ludwigs–Universität Medizinische Fakultät, Giessen, Hesse, Germany, 1893; served on the staff of the Samuel Merritt Hospital; died Dec. 5, aged 94.

Laumann, Thomas Browning, Sulphur, Okla. (licensed in Oklahoma under the Act of 1908); died Sept. 28, aged 92.

Lee, Ralph Everett, Douglaston, N. Y.; Harvard Medical School, Boston, 1904; died Dec. 4, aged 83.

Leonardo, Richard Anthony Ⓜ Rochester, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1919; fellow of the International College of Surgeons; county coroner; veteran of World War I; author of many books; died in a hospital at Hope Mills, near Fayetteville, N. C., Dec. 5, aged 63.

Lewis, James Edward Ⓜ Lieut. Colonel, U. S. Army, Grand Island, Neb.; born in Turtle Creek, Pa., Oct. 12, 1916; University of Pittsburgh School of Medicine, 1941; interned at Western Pennsylvania Hospital in Pittsburgh; veteran of World War II; assistant surgeon of Fifth Army Corps at Fort Bragg and accompanied the unit to Germany in 1951; later assigned to command the 351st Mobile Army Surgical Hospital; later surgeon of the First Infantry Division; last year assigned to Turkey as medical adviser to the Turkish Surgeon General; received the Commendation Medal for meritorius services in Turkey; died in the Walter Reed Army Hospital, Washington, D. C., Dec. 5, aged 43.

Lewis, James Wayne Ⓜ Colorado Springs, Colo.; University of Colorado School of Medicine, Denver, 1936; specialist certified by the American Board of Radiology; member of the Radiological Society of North America, American College of Radiology, and the American Radium Society; formerly vice-president of the Colorado Radiological Society; veteran of World War II; at one time instructor in radiology at Northwestern University Medical School in Chicago; associated with the Colorado Springs Medical Center; consulting radiologist, Colorado State Hospital in Pueblo; died Dec. 14, aged 47.

Lewis, William Benjamin Ⓜ Vallejo, Calif.; University of Colorado School of Medicine, Denver, 1912; veteran of World Wars I and II; died Nov. 28, aged 73.

Lindquist, Carl Augustus Ⓜ Coventry, Conn.; Tufts College Medical School, Boston, 1900; died in Norwich Oct. 13, aged 85.

McGuinness, Madge Carroll Leonard Ⓜ New York City; born in 1884; Woman's Medical College of Pennsylvania, Philadelphia, 1908; specialist certified by the American Board of Physical Medicine and Rehabilitation; member of the American College of Cardiology and the American Academy of Physical Medicine and Rehabilitation; past-president of the New York State Women's Medical Society and won its 1952 award; served as secretary of the Joint Committee in Specialties, comprising pathologists, radiologists, anesthetists, and physical therapists. and the New York Society of Physical Medicine; associated with the Lenox Hill Hospital and the Misericordia Hospital, where she died Dec. 9, aged 75.

Nash, William Gibbs, Ocala, Fla.; Columbia University College of Physicians and Surgeons, New York City, 1903; formerly practiced in Newark, N. J.; died Nov. 15, aged 85.

Natvig, Gerhard Alfred, Prairie Farm, Wis.; University of Illinois College of Medicine, Chicago, 1914; died in November, aged 72.

Nelson, Hiram Milford Ⓜ Santa Cruz, C lege of Medical Evangelists, Loma Linda Angeles, 1932; interned at the Santa Clara C Hospital in San Jose; served a residency at White Memorial Hospital in Los Angeles; veteran of World War II; specialist certified by the American Board of Dermatology; certified by the National Board of Medical Examiners; member of the American Academy of Dermatology and Syphilology; on the staffs of the Santa Cruz County and Sisters hospitals; died Nov. 24, aged 53.

Newell, Harris Andrews, Chicago; Northwestern University Medical School, Chicago, 1909; died Nov. 24, aged 80.

Oglevie, Rial Richardson Ⓜ Kansas City, Mo.; University of Kansas School of Medicine, Kansas City, Kan., 1923; member of the Industrial Medical Association; veteran of World War I; member of the staffs of Queen of the World Hospital and St. Luke's Hospital, where he died Nov. 25, aged 62.

Palmer, Lester Joerg Ⓜ Seattle; Northwestern University Medical School, Chicago, 1914; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; past-president of the American Diabetes Association and of the Washington State Diabetes Association; secretary of the North Pacific Society of Internal Medicine from 1927 to 1947 and president the following year; veteran of World War I; for many years clinical professor of medicine at the University of Washington School of Medicine; chief of services and president of the board of trustees of the Virginia Mason Hospital, of which he was one of the founders, and where he died Nov. 29, aged 69.

Phillips, Harry Shaw Ⓜ Westport, Conn.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1922; for many years medical examiner; veteran of World War II; on the staff of the Norwalk (Conn.) Hospital; died on Cockene Island Dec. 9, aged 64.

Price, Thomas Horner, Philadelphia; Jefferson Medical College of Philadelphia, 1920; for many years on the staff of the Frankford Hospital; formerly associated with Germantown and Lankenau hospitals; died Nov. 25, aged 65.

Raney, Rupert Brandon Ⓜ Los Angeles; born in Loogootee, Ind., Oct. 16, 1900; Creighton University School of Medicine, Omaha, 1927; specialist certified by the American Board of Psychiatry and Neurology and the American Board of Neurological Surgery; served on the faculty of the University of Southern California School of Medicine; member of the American Academy of Neurological Surgery, of which he was past-president, Harvey Cushing Society, and the American Neurological Association; fellow of the International College of Surgeons and the American College of Surgeons; affiliated with the Daniel Freeman Memorial Hospital in Inglewood, St. Joseph Hospital, Burbank, Veterans Administration Hospital in Long Beach, Morningside Hospital, Crenshaw Hospital, Cedars of Lebanon Hospital, Queen of Angels Hospital, Hospital of the Good Samaritan, Hollywood Presbyterian Hospital, and St. Vincent's Hospital; died in Loogootee, Ind., Nov. 28, aged 59.

Raw, Elmer Joseph Ⓜ Pierson, Iowa; born in Council Hill, Ill., May 20, 1874; University of Illinois College of Medicine, Chicago, 1899; served on the school board and the city council; died Oct. 8, aged 85.

Reese, Forrest Leslie Ⓜ Phoenix, Ariz.; University of Illinois College of Medicine, Chicago, 1908; interned at Cook County Hospital, Chicago; served in the Army Medical Corps during World War I; past-president of the Phoenix Lions Club; member of Alpha Omega Alpha; died Oct. 1, aged 74.

Reinhardt, George Herman, Cleveland Heights, Ohio; College of Physicians and Surgeons of Baltimore, 1904; in 1908 medical director for a railroad contractor in Bolivia; served during World War I as a major with the Army Medical Corps; member of the Cleveland Academy of Medicine, which in 1954 honored him for fifty years of professional service; died in Lakeside Hospital, Cleveland, Oct. 4, aged 79.

Ridall, Paul Leslie Ⓜ Williamsport, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1929; veteran of World War I; died in the Williamsport Hospital Nov. 23, aged 62.

Ritchie, Saul Ⓜ Kingston, N. Y.; Tufts College Medical School, Boston, 1925; specialist certified by the American Board of Orthopaedic Surgery; member of the American Fracture Association and American Academy of Orthopaedic Surgeons; fellow of the International College of Surgeons and the American College of Surgeons; veteran of World War II; consultant, North Dutchess Health Service Center, Rhinebeck; member of the staffs of the Hospital of Greene County, Catskill, Margaretville (N. Y.) Hospital, and the Maimonides Hospital, Liberty; associated with Benedictine Hospital, where he died Nov. 19, aged 58.

Robertson, Sylvan Hallas Ⓜ Chicago; Rush Medical College, Chicago, 1933; specialist certified by the American Board of Internal Medicine; member of the American Psychosomatic Society; served on the faculty of the University of Illinois College of Medicine; member of the staff of the Michael Reese Hospital and the Highland Park (Ill.) Hospital, where he died Dec. 7, aged 53.

Rogers, Lawrence H. Ⓜ Trenton, N. J.; New York University College of Medicine, New York City, 1908; for a time practiced in Paterson; medical director and superintendent of the F. W. Donnelly Memorial Hospitals; served with the Army Medical Corps during World War I; past-president of the Mercer County Medical Society; member of Phi Alpha Sigma; died Oct. 14, aged 76.

Ross, Gilson A. Ⓜ Eugene, Ore.; Northwestern University Medical School, Chicago, 1924; interned at Charity Hospital, New Orleans; at one time head of the University of Oregon student medical center; veteran of World War I; fellow of the American College of Surgeons; former mayor of Toppenish, Wash., where he was a member of the Chamber of Commerce and assisted with the organization of Central Memorial Hospital; on the staff of Sacred Heart General Hospital; died Oct. 7, aged 63.

Roy, Leopold Onesime Ⓜ Lewiston, Maine; Laval University Faculty of Medicine, Quebec, Canada, 1906; for a time practiced in Augusta; served with the Army Medical Corps during World War I; past-president of the Androscoggin County Medical Association; past-president of the staff of St. Mary's General Hospital, where he died Oct. 5, aged 79.

Sandidge, Roy Preston Ⓜ Charlottesville, Va.; University of Virginia School of Medicine, Charlottesville, 1914; retired from the U. S. Public Health Service March 1, 1944; died in the Martha Jefferson Hospital Dec. 2, aged 70.

Sawyer, Joseph Harlan, Marshfield, Mass.; Middlesex College of Medicine and Surgery, Waltham, 1931; veteran of World War II; died in the Veterans Administration Hospital, Boston, Nov. 26, aged 57.

Schnaer, Ira Lionelle Ⓜ Skokie, Ill.; Universita degli Studi di Bologna, Facolta di Medicina e Chirurgia, Italy, 1933; served an internship at Edgewater Hospital, Chicago; served as a lieutenant commander in the Navy Medical Corps during World War II; formerly on the faculties of the Chicago Medical School and the University of Illinois; fellow of the American College of Cardiology; on the staff of Presbyterian–St. Luke's Hospital and Edgewater Hospital, where he was former president and chief of staff and member of the executive committee, and where he died Oct. 16, aged 52.

Schreiber, Frederic Ⓜ Detroit; Harvard Medical School, Boston, 1923; specialist certified by the American Board of Surgery and the American Board of Neurological Surgery; member and past-president of the Harvey Cushing Society; past-president of the Detroit Academy of Medicine; fellow of the American College of Surgeons; served on the faculty of Wayne University College of Medicine; associated with the Children's Hospital of Michigan, Highland Park (Mich.) General Hospital, Herman Kiefer Hospital, and the Harper Hospital, where he died Dec. 3, aged 62.

Shepard, Frank Parsons, Greenwich, Conn.; Columbia University College of Physicians and Surgeons, New York City, 1952; interned at Bellevue Hospital, New York City; served residencies at Roosevelt Hospital and Presbyterian Hospital, New York City; served as a captain in the Marine Corps during World War II; assistant professor of pathology at his alma mater; on the board of directors of the Greenwich Chapter of the American Red Cross; died in Greenwich Hospital Oct. 13, aged 39.

Sherrard, John C., Norway, Kan.; College of Physicians and Surgeons, Medical Department of the Kansas City University, Kansas City, Kan., 1905; died in Belleville Nov. 27, aged 81.

Shuffelton, Frank Alby, St. Marys, Ohio; The Hahnemann Medical College and Hospital, Chicago, 1900; served in the Navy Medical Corps during World War I; at one time physician for the Standard Oil Company in Whiting, Ind., and later a resident physician at the St. Charles (Ill.) Hospital; from 1950 to 1957 was civilian medical officer at Fort Knox, Ky.; formerly on the board of education and in 1925 its president; died in Columbia, S. C., Oct. 7, aged 82.

Shulman, Abraham Ⓜ Paterson, N. J.; University and Bellevue Hospital Medical College, New York City, 1918; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; past-president of the Passaic County Medical Society; served as president of the New Jersey State Obstetrical and Gynecological Society; associated with the Barnert Memorial Hospital, where he was past-president of the medical staff; died at his home in East Paterson Nov. 22, aged 62.

Shumate, James William Ⓜ Santa Cruz, Calif.; University of Arkansas School of Medicine, Little Rock, 1929; interned at Kings County Hospital, Brooklyn; specialist certified by the American Board of Orthopaedic Surgery; at one time practiced in San Francisco, where he had been a clinical professor of orthopedic surgery at the University of California School of Medicine; served in the U. S. Navy during World War II; member of the American Academy of Orthopaedic Surgeons; died Oct. 11, aged 56.

Self, Thomas F., Roy, N. M.; Gate City Medical College, Dallas, Texas, 1907; died in the New Mexico Miners' Hospital, Raton, Nov. 25, aged 78.

Simms, Earlin Judson Ⓜ Columbus, Ohio; Ohio State University College of Medicine, Columbus, 1911; member of the Columbus Academy of Medicine; on the staff of Mercy Hospital, where he died Oct. 8, aged 72.

Sinclair, Jardine Frank Ⓜ Chicago; Dearborn Medical College, Chicago; 1907; past-chief of the medical staff of Medinah Temple; formerly on the staff of Alexian Brothers Hospital; died Oct. 20, aged 80.

Stabnick, Joseph Sigmund, Hartford, Conn.; Jefferson Medical College of Philadelphia, 1934; interned at the Reading (Pa.) Hospital and the New York Hospital, where he served a residency; served a residency at the John Gaston Hospital in Memphis, Tenn., and the Hartford (Conn.) Hospital; member of the American Society of Anesthesiologists; associated with the Veterans Administration Hospital in Newington and the Hartford Hospital, where he died Nov. 14, aged 49.

Stanton, Thomas Menees, High Point, N. C.; Medical College of Virginia, Richmond; 1916; during World War I served overseas with Base Hospital 65; died in the Veterans Administration Hospital, Salisbury, Oct. 7, aged 69.

Stofflet, Clinton F. Ⓜ Pen Argyl, Pa.; Medico-Chirurgical College of Philadelphia, 1898; past president and for many years treasurer of the Northampton County Medical Society; member of the board of health of Pen Argyl and public school examiner for many years; during World War II medical examiner for Northampton County Draft Board; on the auxiliary medical staff of Easton (Pa.) Hospital; served as vice-president and director of the First National Bank of Pen Argyl; died Nov. 28, aged 82.

Swierat, John Valentine, Depew, N. Y.; University of Buffalo School of Medicine, 1917; served in the Army Medical Corps; in 1942 was honored by the Medical Arts Society, of which he was a member, for twenty-five years of professional service; served as psychiatric consultant to various institutions in Cheektowaga and Amherst; on the staffs of Millard Fillmore, Mercy, and Sisters of Charity hospitals, Buffalo; died in Buffalo Oct. 8, aged 65.

Tackaberry, Arthur Lee Wilson Ⓜ Santa Monica, Calif.; Medical Department of Tulane University of Louisiana, New Orleans, 1896; formerly medical officer for the Ford Motor Company assembly plant in Houston, Texas; died Nov. 28, aged 85.

Tappan, Benjamin Ⓜ Baltimore; Johns Hopkins University School of Medicine, Baltimore, 1915; consulting physician at Johns Hopkins Hospital, Kernan Hospital, and St. Joseph's Hospital; visiting pediatrician at Union Memorial Hospital and Church Home and Hospital; died Dec. 30, aged 69.

Thieda, Arthur Alexander Ⓜ Cicero, Ill.; Rush Medical College, Chicago, 1930; interned at St. Mary of Nazareth Hospital, Chicago; member of the American Academy of General Practice and the Polish Medical Society; former medical director and health commissioner; on the staff of St. Mary of Nazareth Hospital, where he taught in the nurses training school and where he died Oct. 21, aged 54.

Toland, Joseph James Jr. Ⓜ Philadelphia; Medico-Chirurgical College of Philadelphia, 1912; interned at Frankford Hospital; fellow of the International College of Surgeons, the American College of Surgeons, and the College of Physicians of Philadelphia; served as chairman of the committee on legislation in the Philadelphia County Medical Society; served in the Navy Medical Corps during World War II; director of the Northeast National Bank; in November, 1958, received the first award of merit from the alumni association of his alma mater; received the nineteenth annual Signum Fidei Award from the Alumni Association of LaSalle College; in December, 1958, he was chosen outstanding Catholic physician of the year by the National Federation of Catholic Physicians Guilds, of which he was a past-president; also past-president of the Men of Medical Missions; surgeon and first commander of the Frankford American Legion Post; former medical director and chief of surgery at Nazareth Hospital; former chief surgeon at the Pennsylvania State Hospital, Byberry; died in the Temple University Hospital, Oct. 19, aged 72.

Veeder, Willard Hall Ⓜ Geneseo, N. Y.; University of Buffalo School of Medicine, 1903; specialist certified by the American Board of Psychiatry and Neurology; past-president of the Medical Society of the County of Monroe; past-vice-president of the Rochester Academy of Medicine; veteran of World War I; for many years on the staff of the Rochester State Hospital; retired superintendent of the Craig Colony at Sonyea; died in the Peterson Hospital at Sonyea Dec. 5, aged 80.

Vogelsang, Aaron Dewey Ⓜ Toledo, Ohio; Ohio State University College of Medicine, Columbus, 1922; specialist certified by the American Board of Urology; member of the American Urological Association; fellow of the American College of Surgeons; past-president of the Toledo Academy of Medicine; veteran of World War II; on the staffs of the St. Vincent's, Toledo, Flower, and Maumee Valley hospitals; died Nov. 29, aged 62.

Watson, Clyde Otis Ⓜ Corpus Christi, Texas; University of Louisville (Ky.) School of Medicine, 1908; twice served on the city council; member of the school board for ten years; on the staff of Spohn Hospital; died Oct. 6, aged 78.

Waugh, Henry Hartzell Ⓜ Dover Plaines, N. Y.; University of Wooster, Medical Department, Cleveland, 1891; specialist certified by the American Board of Ophthalmology; fellow of the American College of Surgeons; for many years practiced in Brooklyn, where he was a member of the board of trustees and senior surgeon of the Brooklyn Eye and Ear Hospital; died Oct. 5, aged 91.

West, Arthur Dudley Ⓜ Moline, Ill.; University of Vermont College of Medicine, Burlington, 1898; veteran of World War I; died Nov. 25, aged 86.

Wiginton, Marquis Claude Ⓜ Hammond, La.; Northwestern University Medical School, Chicago, 1924; member of the American Academy of General Practice; past-president of the Louisiana Academy of General Practice and the Tangipahoa Parish Medical Society; associated with the Wiginton Memorial Hospital; died in Indian River City, Fla., Nov. 25, aged 64.

Willcox, William David Ⓜ Fitzgerald, Ga.; Emory University School of Medicine, Emory University, Ga., 1937; veteran of World War II; formerly on the board of education; on the staffs of Ben Hill County Hospital; died Oct. 1, aged 47.

Woodcock, Charles Edwin Ⓜ Greenwood, Ind., Indiana University School of Medicine, Bloomington–Indianapolis, 1915; interned at Indianapolis City Hospital; for a time practiced in Zionsville; during World War I served with the Army Medical Corps and went to Siberia with Evacuation Hospital 17; member of the Chamber of Commerce; died Oct. 2, aged 72.

Wyatt, Kon Ⓜ Canon City, Colo.; University of Virginia School of Medicine, Charlottesville, 1920; past-president of the Fremont County Medical Society; veteran of World Wars I and II; bank president; associated with St. Joseph Hospital in Florence and St. Thomas More Hospital; served as county coroner; past-president of the Canon City Chamber of Commerce; died Nov. 28, aged 63.

Young, Armanus Hixon, Pomona, Calif.; born in Highland County, Ohio, Oct. 17, 1861; Iowa Eclectic Medical College, 1888; at one time practiced in Oklahoma; died in Ontario, Calif., Oct. 2, aged 97.

Young, Samuel A., Anaheim, Calif.; State University of Iowa College of Medicine, Iowa City, 1896; died Oct. 3, aged 89.

Zvaifler, Nathan Ⓜ Newark, N. J.; Jefferson Medical College of Philadelphia, 1917; interned at St. Michael's Hospital, Newark; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; past-president of the Newark Beth Israel Hospital staff and the Northern New Jersey Jefferson Medical College Alumni Association; member of the New Jersey Society of Surgeons and Phi Delta Epsilon; consultant to Martland Medical Center, Presbyterian Hospital, and Irvington General Hospital; died in East Orange Oct. 18, aged 65.

FOREIGN LETTERS

DENMARK

Spastic Paraplegia.—Pedersen and Schleisner (*Acta psychiat. et neurol. scandinav.* 34:342-353, 1959) reported that bis (4, 6 diethylamino-1,3,5-triazino-2-yl) hydrazine dihydrochloride (Ciba, 13,155), a new muscle relaxant, exerts its action by depressing the polysynaptic pathways. The effect of the drug was studied in 50 patients, most of whom had spastic paraplegia. It was effective when given orally and during an experimental period of seven months did not give rise to serious side-effects. The authors advised against a rigid dosage schedule but stated that the treatment might be started by giving a patient weighing 60 to 70 kg. (132 to 154 lb.) an initial dose of 50 mg. three times daily. The drug proved to have an excellent effect on difficulties in bladder control, especially in reducing pollakiuria and incontinence. In about one-half of the patients appreciable relaxation of muscular tone was obtained, with subsequent improvement of the gait.

Electroencephalography was performed before the institution of treatment with the drug and two or three times later, as far as possible when the patient was on the largest dosage schedule. Changes were observed in seven patients; slow activity was slightly increased in four, moderately increased in two, and returned to normal in one. The drug appeared to have certain features in common with zoxazolamine, but the latter does not improve volitional control, and its value has been further questioned in recent reports. Ciba 13,155 was undoubtedly superior both to mephenesin, which must be administered intravenously for maximum benefit, and to curare, which has a narrow margin of safety.

Imipramine for Endogenous Depressions.—Andersen and Kristiansen (*Acta psychiat. et neurol. scandinav.* 34:387-397, 1959) used imipramine to treat 85 patients who had endogenous depressions. The drug was given in 25-mg. tablets and intramuscularly. Both peroral and combined peroral and parenteral treatment were used, the latter in patients with severe depression. There was no appreciable difference between the effects of these two methods. Improvement commenced usually in the second or third week of treatment. The depressions were cured or ameliorated in 80% of the patients. There were no deaths, and no patient's condition deteriorated. Good results were obtained, and treatment could be terminated in about 50% of patients after four weeks or less of treatment. In most patients there was profuse perspiration, slight decrease in blood pressure, tremor, dry mouth, and disturbances of visual accommodation, but these disturbances were usually not serious. There were two cases of temporary icterus, three of short-lived delirium, and one of transient mania. Mild withdrawal symptoms were noted in 15 patients, but the authors did not observe euphoria or addiction. The authors concluded that imipramine is a promising antidepressive but that caution should be exercised when it is given to elderly patients or patients with increased blood pressure.

Therapeutic Use of Lithium.—Mogens Schou (*Acta psychiat. et neurol. scandinav.* [supp. 136] 34:51-55, 1959) gave lithium to 157 patients suffering from mania. Within two or three weeks after the start of the treatment, improvement or recovery was observed in 122 patients (about 80%). Doses of 1 to 2 Gm. per day were given to patients suffering from the manic phase of manic-depressive psychosis. Controlled studies indicated that, in at least 50% of these patients, the improvement was due to the lithium and not to spontaneous remission, suggestion, or inaccuracies of clinical observation. The author believed lithium treatment to be preferable to electric convulsive therapy and to other drug therapy in patients with protracted or frequently recurring mania. It was ineffective during depression. Lithium is potentially toxic, but the toxic effects may be checked and the drug used safely in controlled doses if the patients ingest a sufficient amount of sodium. Animal experiments have shown that the principal toxic action of lithium is on the kidney tubules. Sodium protects patients against toxic injury through a competition with lithium for entrance into and reabsorption through the tubule cells.

Perphenazine.—The results of nine months medication with perphenazine in a series of 309 patients with mental disease were analyzed by Gustav Hansen and co-workers (*Acta psychiat. et neurol. scandinav.* [supp. 136] 34:78-81, 1959). In this series 183 patients had previously had electroshock therapy, 108 had been treated with insulin coma, and 36 had each had a lobotomy. A total of 285 patients received no other treatment while the perphenazine was being given, and the rest had

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The items in these letters are contributed by regular correspondents in the various foreign countries.

supplementary treatment with electroshock, reserpine, or meprobamate. The series comprised 295 chronically and 14 acutely ill patients, 63% of whom were schizophrenic. Thus the majority were in the older age groups. Among the 285 who received perphenazine alone 16.1% were much improved, 29.5% were slightly improved, 49.5% showed little or no improvement, and 4.9% became worse. The results in the 24 patients who received supplementary treatment showed a similar distribution. Thus in the entire series 45.7% obtained improvement. One reason why the results were not better was probably that the series consisted of patients who had shown little response to other therapeutic measures. Side-effects occurred in 187 patients and consisted primarily of parkinsonism, fatigue, and drowsiness.

FINLAND

Contrast Examination of Lumbar Interspinous Ligaments.—Rolf Köhler (*Acta radiol.* 52:21-27, 1959) described a method for roentgenographic examination of the lumbar interspinous ligaments based on the injection of a contrast medium close to the ligaments on both sides. He examined a series of 100 patients with low backache or sciatica by this method. Bilateral injection of the contrast medium gave a more complete result than unilateral injection on the side of the patient's main symptoms. Because it is more concentrated than monoiodized water-soluble preparations (20%) a preparation such as 30% Urografin improved the quality of the film of the last 10 patients on whom it was used. In roentgenograms of normal persons the ligament appears as a flat spindle-shaped filling defect bounded by contrast medium. In pathological cases the contrast medium penetrates into the ligament through defects.

Of the 100 patients examined, 55 were operated on, the majority because of a diagnosis herniated nucleus. The roentgenographic findings corresponded well with the operative findings in patients in whom the contrast medium had been correctly deposited close to the ligamentous wall. Of the 55 surgically treated patients, 19 had normal ligaments in the L-3 to L-5 interspinous spaces. In 1 patient a herniation was seen in the L-3 to L-4 space, in 10 in the L-4 to L-5 space, and in 4 in the L-5 to S-1 space, while 3 had symptoms of sciatica without herniation.

Working Capacity of Uninsured Seriously Disabled Persons.—Kauko A. Solonen (*Ann. chir. et gynaec. Fenniae* 48:115-129, 1959) reported on a series of 17 uninsured patients who were able to work hard at jobs that often seemed especially strenuous in view of the patients' defects. The subjects included three with tuberculous spondylitis, three with arthrosis of the hip joint, two with pseudarthrosis of the olecranon, and one each with ankylosis of the wrist, destruction of the hip joint and marked shortening of the lower extremity, pseudarthrosis of the neck of the femur, pronounced traumatic deformation of the talocural joint and pseudarthrosis of the fibular malleolus, tuberculous coxitis, pseudarthrosis of the carpal navicular and carpal tunnel syndrome, osteosarcoma of the femur (this patient resumed his former occupation immediately on discharge from hospital three weeks after amputation), a malignant growth in the soft part of the ankle, and destruction of the hip joint as a result of a gunshot wound. Several of the patients were farmers who worked their own farms. All were engaged in heavy manual work and were well adapted to their environment. Their intelligence was average or above. They all had to work but appeared to enjoy their work.

The author observed that a young person adapts himself more easily to his trauma than an old person, but an intelligent old man or woman understands instinctively the naturalness of the limitations of age and is not depressed when they are felt. In the absence of insurance protection man makes the best possible use of his own physical and mental capabilities. The mobilization of these faculties is also affected by many other factors: individual characteristics; mode of life; social, economic, and home life; and emotional experience. The favorable effect of mental and physical activity and work was revealed by these patients. All these aspects should be considered. The patients should be treated as normal human beings.

Congenital Clubfoot.—Solonen and Parkkulainen (*Ann. chir. et gynaec. Fenniae* 48:130-140, 1959) reported that of the 134 patients with congenital clubfoot treated at the department of pediatrics of the Central University Hospital in 1947-1953, 74 were given a follow-up examination in 1957-1958. The final results were good in 51%, fair in 30%, and poor in 19%. In 34 patients with bilateral clubfoot the result recorded was that of the worse foot. The results were usually the same for both feet. Recurrences after inadequate primary treatment were seen in several patients. Insufficient or delayed primary therapy was the most important reason for the poor final result, although the results were also affected by the primary degree of difficulty of the deformity. Neglect of further therapy resulted in recurrences. The great number of recurrences was the reason for the exceptionally great number of operative measures (62% of the total number of patients).

The most troublesome of the residual deformities were talipes varus and talipes equinus, usually the most difficult components. The other components of the primary deformity were less troublesome. Treatment provoked such deformities as transversoplanus, rockerfoot, and planovalgus of the originally healthy foot. Early and intensive primary treatment and carefully supervised and controlled further treatment of long duration were the best guarantees of good results. The principal object of primary treatment must be correction of the most difficult deformity components, varus and equinus. If this treatment does not prove successful early achillotenotomy might be advisable.

Effect of Psychic Tension on Capillary Resistance.—The capillary resistance of 47 medical students was measured by Panu Hakola and co-workers during and after psychic tension due to a test (*Ann. med. exper. et biol. Fenniae* 37:314-319, 1959). That of 10 inmates of a mental hospital was also measured. Capillary resistance was observed to be higher when the subjects were under tension. The increase in capillary resistance was slightly greater in those who exhibited the lowest capillary resistance level when not excited. The increase was also found to be greatest in those with the quickest pulse during the tension. The average increase of capillary resistance during the tension was 2.23 cm. Hg, and there were differences between the student group and the inmate group, the average being 1.9 cm. Hg for the students and 3.8 cm. Hg for the inmates. Electric shock was the only other stimulus observed to produce an increase in capillary resistance in subjects in whom a decrease had been noticed when the general nervous system was stimulated mechanically, by means of x-rays, or after a concussion of the brain.

The authors concluded that it was possible that psychic tension influenced capillary tension through the increasing effect of the added epinephrine content of the tissues on the capillary resistance. This conclusion was supported by the fact that capillary resistance, increased by psychic tension, might decrease almost instantaneously. This phenomenon was observed when the tension was due to the subject's fear of the capillary resistance measurement, and it disappeared as soon as the measurement proved to be completely painless and harmless.

Delayed Effects of Brain Trauma.—Eero Hillbom examined a series of 3,552 patients with brain injury incurred in World War II (*Acta psychiat. et neurol. scandinav.* [supp. 137] 34:7-29, 1959). In 18.8% the injury was mild, in 59.3% it was moderate, and in 21.8% it was severe. Of the injuries 61.1% were caused by shell splinters, 22.7% by bullets, and 16.2% by other agents. The author made a detailed analysis of 415 of these patients. Frontal and facial injuries were comparatively frequent among the mildly injured, and the frontal injuries were fairly frequent among the severely injured. On the other hand sensorimotor injuries were very frequent among the severely injured. Pareses and disturbances of the tactile sense were most often the most serious symptoms causing disability. Disturbances of the tactile sense occurred in 109 patients. Ataxias and symptoms of metabolic and cardiovascular dysfunction were relatively frequent. Traumatic epilepsy was found in 41.5% of all the patients and in 70% of the severely injured patients. The more severe the injury the more diversified were the associated symptoms. Delayed psychotic complications were observed, particularly in those with temporal injuries. Severe changes of personality and epileptic attacks resembling hysteria were observed especially in those with frontal injuries.

Funnel Chest.—Tala and Laustela (*Ann. chir. et gynaec. Fenniae* 48:177-188, 1959) performed 18 operations on 16 patients for the correction of funnel chest. Their patients' ages ranged from 3 to 37 years. In all these patients the deformity was observed soon after birth. No subjective symptoms were attributable to the deformity in the children, but displacement of the heart to the left was found roentgenographically in two of them. On the other hand the adults had severe symptoms. Displacement of the heart to the left or compression was noted in all the adults. These patients also had a sternal depression of much greater degree than did the children, and it was asymmetric in most cases. Cardiorespiratory disturbances were frequent. Patients complained of palpitation, dyspnea on exertion, and precordial pain. Pulmonary insufficiency of a mild degree was noted in three patients.

The results of the operation were good in all patients, but the results were much better in the children than in the adults. The treatment was in part conservative and in part surgical. One of the most recent operative techniques consists of dividing the attachments of the xiphoid and osteotomy of the anterior cortex of the body of the sternum with elevation of the gladiolus. Several modifications of this procedure, such as fixation of the elevated sternum to an external splint or prosthesis or internal fixation with grafts of rib, cartilage, wires, or Steinman pins, were used.

Children were treated differently from adults. Correction of pectus excavatum of children required less effort, and the hazard was relatively negligible. The ideal age for operation is 4 years. The operation may then be performed by resecting the xiphoid cartilage and severing the fibrotic attachments between diaphragm and sternum. In the present series good cosmetic results were obtained in all patients below 15 years of age with the use of the above-mentioned operative technique, whereas in the group of adults the results were merely satisfactory in four of nine patients, whose sternum, which had a highly asymmetrical depression and rotation, could not satisfactorily be brought into the normal plane. However, these patients were satisfied with the results.

Staphylococci in Mother's Milk.—Rantasalo and Kauppinen (*Ann. chir. et gynaec. Fenniae* 48:246-258, 1959) subjected milk samples from mothers to bacteriological study. The series comprised 88 mothers delivered in hospital in 1951, 84 mothers delivered in hospital in 1957, and 36 mothers who gave birth at home in 1952. On the fifth postpartal day *Staphylococcus aureus* was found in the milk of about 50% of the parturients in institutions but in the milk of only 28% of mothers delivered at home. The incidence of mastitis was greater in parturients in institutions than in those at home (7% and 0%). The Staph. aureus strains found in the milk of mothers delivered at home were generally responsive to antibiotics. Staph. aureus strains resistant to antibiotics were much more common in institutional parturients, and this resistance became far more frequent during the six years of the investigation.

The prophylactic use of penicillin in institutions could not prevent the infection of mother's milk by Staph. aureus or decrease the incidence of mastitis. Other antibiotics would presumably also be ineffective, since resistant strains developed to all the antibiotics studied. This development was slowest with chloramphenicol but very rapid with streptomycin and the tetracyclines. The mothers generally contracted the Staph. aureus infection first and then transmitted it to their babies through milk. Although Staph. aureus strains resistant to various antibiotics developed more slowly at home than in hospital, it was advisable also in the home to avoid using rarer antibiotics in order to prevent the development of resistant strains, especially as staphylococcic infections in homes were generally sensitive to penicillin, streptomycin, and the tetracyclines.

Use of Hydroxydione in Cesarean Sections.—Kivalo and Tammisto (*Acta anaesth. scandinav.*, supp. 2, pp. 35-40, 1959) used hydroxydione as an anesthetic for cesarean section in a series of 65 mothers. The total dose for induction was 1.0 to 1.5 Gm. supplemented after the delivery by nitrous oxide and oxygen. In order to determine the most suitable application of the drug they used (1) hydroxydione alone, (2) hydroxydione with d-tubocurarine, and (3) hydroxydione with succinylcholine. The induction of the 11 patients in the first group took, on the average, nine and one-half minutes and proved entirely unsuitable, as patients responded violently to the incision. Of the babies 27.3% suffered from asphyxia immediately after birth but were cured with electric shock. In the 33 patients of the second group only 6 were adequately anesthetized, and in the remaining 27 patients movements of the body interfered with the operation. All 21 persons in the third group were successfully anesthetized. The authors concluded that the administration of the larger doses of hydroxydione resulted in a higher frequency of neonatal asphyxia and the slower recovery of the infants. The drug, however, may be recommended for preeclamptic and diabetic patients. In emergency sections necessitated by fetal asphyxia, premature separation, etc., when induction must be as rapid as possible, hydroxydione was inferior to other anesthetics.

New Steroid.—A new synthetic steroid, 6 α-chloroprednisolone, has a potent antirheumatic and antipyretic effect. Kalliomäki and Häkkinen (*Acta endocrinol.* 32:59-62, 1959) used it to treat a series of 15 hospitalized patients who had rheumatoid arthritis. It was found that the improvement in these patients which was obtained with 15 mg. of prednisolone a day could be maintained with 12 mg. of the new drug. During treatment with 6 α-chloro-prednisolone no tendency for sodium retention, potassium loss, hyperglycemia, changes in serum inorganic phosphorus, weight change, blood pressure elevation, and gastric or psychic disturbances were observed. The rebound phenomenon could also be observed after cessation of treatment with the new drug.

FRANCE

Vibration Therapy for Psychosomatic Disorders.—At the meeting of the French Society of Psychosomatic Medicine in October, P. Strouzer and A. Albert reported the results of treatment with vibrations in a series of 206 patients. The patients were placed in recumbent position on a vibrating table. The head rested on a platform that did not vibrate. The frequency of the vibrations ranged from 12 to 50 cycles per second. A definite improvement was recorded in 19 patients with post-traumatic sequelas of occupational accidents; in 17 patients with sequelas of cranial trauma with or without fracture, comprising such syndromes as right hemiplegia and facial paralysis; and in 22 of 44 women with cellulitis. In 13 of 42 psychotics with neuroses, an improvement was observed in the neuroses but not in the psychosis. In general, euphoria was observed, and, in particular, a transitory or definitive tendency to improvement of insomnia was noted in those patients in whom no improvement had resulted from other forms of treatment.

A similar effect was recorded in a group of 11 patients (including one with chronic chorea, one with paraplegia, one with a phantom limb, one with paralysis agitans, one with facial hemispasm, and one with epilepsy), but there was no improvement in the underlying disease. In certain hypotensive patients a mild increase in pressure was noted. In patients with mild hypertension a significant and permanent drop of the systolic and diastolic pressure was observed. The speakers gave 10 to 12 sessions of vibration therapy at a rate of 3 sessions per week.

Renal Diseases and Polyarthritis.—E. Berthoud (*Rev. rheumatisme,* no. 2, 1959) reported that in a series of 57 patients treated for chronic progressive polyarthritis 32, in whom the duration of the disease varied from 1 to 35 years, showed no renal lesions. In the remaining 25 patients, in whom the duration of the disease averaged 42 years, temporary or discrete renal changes such as insufficiency on functional tests, increased arterial tension, temporary proteinuria, leukocyturia, or cylindruria were observed. These were not believed to be due to the disease but to the use of acetophenetidin or to that of chrysotherapy with its renal toxicity, even in those who appeared to tolerate this treatment well.

INDIA

Health Priorities.—The Regional Director of WHO for South-East Asia reported (*Antiseptic,* vol. 58, Nov., 1959) that a stricter order of public health priorities should be followed by India and other countries in the southeastern part of Asia in the use of their limited supply of men and material. Because of a shortage of qualified doctors, new medical schools have been opened and the admissions to existing schools doubled, but adequate teaching staffs have not been provided. The result may be a vast number of inadequately trained doctors. One source of relief for the acute shortage of doctors and nurses would be greater use of auxiliary medical personnel. Domiciliary midwifery should be encouraged. The growing tendency for even normal deliveries to be made in hospital is most uneconomical. Rural health centers must devote more effort to preventive measures. Far too little has been done at these centers to improve sanitation or to provide health education, especially in nutrition.

Acetazolamide for Epilepsy.—K. Bhaskaran and co-workers gave acetazolamide to six patients with epilepsy who had proved refractory to the usual anticonvulsant treatment (*J. Indian M. A.,* vol. 33, Nov. 1, 1959). These patients had been suffering from fits for 2 to 36 years. Acetazolamide in doses of 250 mg. three times a day was added to the routine therapeutic regimen. The response was excellent in the four patients with idiopathic epilepsy. In one patient who had petit mal the total number of attacks, which was 540 in the three months preceding the trial, decreased to 4 in the next three months. In the three who had grand mal the number of fits before the trial was 34, 14, and 17, and after the addition of acetazolamide these decreased to 3, 3, and 6 respectively. In the patients with postencephalitic epilepsy and the one with posttraumatic epilepsy there was no appreciable improvement.

Tuberculous Meningitis.—Shah and Bhavsar (*J. Indian M. A.* 33:9 [Nov. 1] 1959) studied a series of 77 patients with tuberculous meningitis—10 in the early, 54 in the intermediate, and 13 in the advanced stages. All patients were given specific antituberculosis treatment in addition to supportive treatment with cod liver oil, vitamins, and symptomatic measures; 43 received streptomycin and isoniazid; 27 received streptomycin, isoniazid, and steroids; 2 received streptomycin intrathecally in addition to injections of streptomycin and isoniazid; and 5 received streptomycin with other antibiotics. In the latter patients the diagnosis was not proved, and these patients died or were taken out of the hospital against medical advice.

Of the 77 patients, 18 were moribund on admission and died. Of the remaining 59 patients, 56 responded well to treatment. The results of treatment were best in patients who came in the early stage. The mortality in those who came in the advanced stage was 54% and of those who came in the intermediate stage 23%. Of the patients who had meningitis alone 70% survived, but of those who also had associated tuberculous lesions 81% survived. If only the patients with advanced cases are considered, 47% of those with meningitis alone and 55% of those with associated lesions failed to respond to treatment. The addition of isoniazid to the therapeutic regimen of these patients changed the course of this grave disease. Most patients who come early enough for treatment can be expected to recover on therapy with streptomycin and isoniazid. In advanced cases, the failure of treatment was 52% in those to whom steroids were not given but only 42% in those to whom they were given. Thus corticosteroid therapy was of definite help in the treatment of patients with advanced cases.

Corneal Xerosis.—K. Bagchi and co-workers (*J. Indian M. A.,* vol. 33, Nov. 16, 1959) stated that xerosis of the cornea is usually believed to be a manifestation of vitamin A deficiency. More recently, protein malnutrition has been found to play some part in precipitating or aggravating vitamin A deficiency, especially in regard to ocular lesions. The authors studied 46 patients with corneal xerosis. They found that brown or muddy pigmentation of the sclera, whether generalized or patchy, has a close relation to nutritional deficiency and corneal xerosis. Thus in six patients xerosis was seen in only one eye, but the other eye had a comparable area with brown pigmentation. These triangular patches cleared with treatment even before improvement began in the xerosis. The latter usually took a long time to clear.

A number of children with protein deficiency were also found to have pigmented patches in both eyes in areas which were in many cases the site of xerosis. These patches cleared up after protein therapy, but in the children who did not receive such treatment the patches gradually became xerotic. If the xerosis was due only to vitamin A deficiency, the absence of other associated manifestations of this deficiency in most of these patients would be surprising, for only four showed night blindness while a large percentage showed evidence of protein deficiency. This finding suggested that protein deficiency played a part in the development of this lesion. One group of these patients received vitamin A by mouth in doses of 50,000 I. U. daily, and the rest received the vitamin in the same dosage and skimmed milk powder which supplied them with 30 Gm. of protein daily. The clinical response took about six months to appear when vitamin A was used alone, but when protein was supplied in addition the response was prompt. Rapid improvement occurred not only in the eye lesions but also in the patients' general condition.

Dacryocystography.—D. P. Aggarwal (*Indian J. M. & Surg.* 24:6 [June] 1959) stated that dacryocystography is useful mainly in determing stenosis or obstruction of the nasolacrimal duct. The exact site of obstruction and position of the lacrimal sac can thus be visualized and the correct line of treatment planned. It is also helpful in evaluating the results of operations. The author used neohydriol, a contrast medium containing 40% iodine. It was easy to inject because of its low viscosity. With its use even small irregularities in the outline of the lacrimal passage could be demonstrated. No undesirable side-effects were observed. Of the 25 patients treated by dacryocystorhinostomy after preliminary visualization by this method, 20 became symptom-free after the operation.

NORWAY

Fat Embolism.—Dr. E. Ofstad (*J. Oslo City Hosp.*, vol. 9, October, 1959) reported a series of 25 patients (21 men and 4 women) who had fat embolism after injury. In 14 the injury was due to a traffic accident. The interval between the injury and the onset of symptoms indicative of fat embolism varied from 20 minutes to seven days. In two patients, who died 45 minutes and 10 hours, respectively, after the injury, small amounts of fat were found post mortem in the cerebral vessels. This finding shows that fat emboli may occur in the systemic circulation soon after an injury. The length of survival of the patients after the injury was from 45 minutes to seven days. Though it is generally assumed that fat embolism usually follows fracture of the long bones, the present series showed that cancellous bones may also yield fat emboli in elderly persons. In three patients the major injury was pelvic fracture in addition to soft tissue injury. The author concluded that pulmonary fat embolism is probably of little clinical importance except in persons with impaired cardiorespiratory function. He also found that petechial hemorrhages provide an important clue to the diagnosis of this condition.

More Doctors Needed.—The dismal forecast of a glut of doctors in Norway in the near future was emphatically denied by Dr. H. Seyfarth (*Tidsskr. norske laegefor.*, Nov. 1, 1959), who believed that the concept of psychosomatic disease has done much to challenge the school of medicine which thinks and teaches exclusively in terms of morbid anatomy. The implications of this teaching led to an oversimplification of diagnosis which eased the task of the doctor. Now that he has learned to recognize psychosomatic disease he can no longer dismiss a headache as a nosological entity but must spend time unraveling the chain link by link. Unfortunately he is himself often the victim of overwork and not mentally fresh enough to tackle this problem well. If there were more physicians it would surely help him to lead a less hectic life and to give his patients better service.

Bromide Psychosis.—Although bromides have largely been replaced by modern sedatives, bromide psychoses still occur occasionally. Between 1951 and 1959 three patients with this psychosis were observed at the Gaustad Mental Hospital to which they had been admitted from other hospitals where it had not been properly diagnosed. K. Noreik (*Tidsskr. norske laegefor.*, Nov. 1, 1959) pointed out that the most conclusive diagnostic test in this ailment is the test for bromide in the serum. The findings were 302, 171, and 189.6 mg. per 100 ml., respectively, in these patients. All of them suffered from delirium and hallucinations, with disturbances of balance and dysarthria. All three had been addicted to alcohol and barbiturates, and all three recovered completely in a few weeks on the withdrawal of bromides and the regulation of fluid intake. Two of them were given sedative doses of insulin. Isotonic sodium chloride solution was given intravenously for four days to one patient.

SWEDEN

Hormone Production of the Placenta.—Under physiological conditions it is difficult to assess adequately the placental elaboration of estrogens and progesterone because of the existence of the fetus. However, a new method for the interruption of pregnancy through artificially induced fetal death (interruption of the connections between the fetus and placenta) offers a suitable means of studying the endocrine functions of the placenta isolated in situ. Ove Cassmer (*Acta endrocrinol.* [supp. 45] 32:7-82, 1959) reported hormone assays of 46 physically healthy patients before and after surgical interruption of their pregnancies. All but two were in the 17th to 21st week of gestation. One-stage and two-stage operations were performed. In the first type the placenta and fetus were completely removed after hysterotomy. In the second type fetal death was induced by interrupting the connections between the fetus and placenta, and the placenta was left in situ. The operation was completed after three days with removal of the placenta and macerated fetus. In a control group of 18 women only artificial rupture of the membranes was performed.

The human chorionic gonadotrophin (HCG) concentration in urine in three of the patients who had the two-stage operation indicated that the interruption of the connections between the fetus and placenta did not interfere with the placental elaboration of HCG. In 11 patients artificially induced fetal death resulted in a slight but significant drop of urinary pregnanediol excretion. On the subsequent three days the pregnanediol excretion remained unchanged, whereas after the complete removal of the placenta and macerated fetus a greatly diminished excretion was observed. In 10 patients the one-stage removal of the placenta and fetus resulted in an immediate marked decrease in the urinary pregnanediol excretion.

In 19 patients artificially induced fetal death resulted in a decrease in all estrogen fractions studied to 46% of the preoperative level. During the subsequent period with the placenta isolated in situ, the excretion further decreased although at a much slower rate. After complete removal of the placenta and macerated fetus the estrogen excretion showed a much more rapid elimination and dropped within three days to normal levels. The disappearance rate of total estrogens, which was estimated before and after complete removal of the products of conception, showed a significant increase.

In 18 patients who had the one-stage operation the estrogen excretion dropped to about 10% of the preoperative level after removal of the fetus and placenta and returned to the normal level within three days. The disappearance rate of total estrogens did not differ from that obtained by the two-stage operation. Statistical analysis of the control series revealed that rupture of the membranes did not interfere with the urinary estrogen excretion.

Allantoin and Psoriasis.—C.-G. Herdenstam (*Acta dermat.-venereol.* 39:216-224, 1959) conducted double-blind tests on 22 patients who had psoriasis with symmetrical bilateral skin lesions in order to study the topical effect of allantoin-petrolatum, allantoin-tar lotion, and allantoin-tar ointment. In six patients the effect of the allantoin-tar ointment was compared with the effect of a 0.25% anthralin ointment. The observed differences between the left and the right side in these patients were not significant, although a more rapid clearing of the skin was noticed on the side where the placebo was applied. The tar preparations were more effective than the petrolatum preparations.

Angiography of Cerebral Arteries.—Georg-Fredrik Saltzman (*Acta radiol.* 52:1-20, 1959) investigated the reason why the posterior communicating artery was visible by carotid angiography in only about one-third of the examinations in which the necessary anatomic conditions for the free passage of the contrast medium were present (354 times in 1,020 carotid angiographies). The posterior cerebral artery was visible less often in the youngest patients and most frequently in middle-aged patients. The incidence dropped again slightly in the higher age-groups. The author concluded by making the following suggestions as to how best to demonstrate the posterior cerebral artery. 1. An attempt should be made to puncture the internal carotid artery. 2. The examination should be in the form of a rapid serial angiography. 3. The contrast medium should be injected rapidly (a short needle might be used in order to reduce the resistance on injection). 4. Puncture complications should be avoided as far as possible (in practice this means that an experienced operator should perform the puncture if demonstration of the posterior cerebral artery is of special importance). 5. The vertebral artery might be compressed.

UNITED KINGDOM

Noise in the Hospital.—Dr. Cecily Statham at the Royal Northern Hospital in London, which is in an area of heavy traffic, questioned 114 patients on noise in the hospital and correlated these findings with a detailed picture of the background noise or quietness of their home and work. Half the patients did not complain of the noise at all. The other half said that certain hospital noises disturbed or worried them. In this group the sex distribution was equal. Patients with noisy surroundings, either in the home or at work, made fewer complaints than those with quiet backgrounds. Patients under 21 and over 65 years of age complained more than those in the intermediate age group, and those in single rooms complained more than those in large wards.

The hospital noises that disturbed patients most were made by other people talking, snoring, and calling out, particularly at night and early morning, and to a lesser extent by the voices of the nursing staff. About half the noise was made by people. The internal hospital noises that worried patients and accounted for 25% of the total noise were the banging of doors, clanking of bed pans, dropping of things on the floors in wards and corridors, the noise of carts, bells, buzzers, elevator gates, and the scraping of chairs, tables, and beds on the floor or wall. External noises, which caused about 25% of the complaints, were mainly due to traffic, in particular the sudden explosive acceleration of motorcycles. One patient used ear plugs at night to deaden the noise.

From these observations the following recommendations were made. When possible patients who are restless, talkative, senile, or disturbing to others should be placed in a single room or small ward. Single rooms should also be used for patients with headache or conditions which make them likely to be distressed by noise. Doors, carts, appliances, and elevator gates should be checked for quiet working. All movable furniture should be fitted with buffers and nurses should be instructed not to cause clatter with bed pans. Future hospitals should be located away from main roads. Wax ear plugs should be provided for those susceptible to noises at night.

Antibiotics and Hospital Infection.—An important contribution to the problem of antibiotic-resistant staphylococcic infections in hospitals was reported by Dr. Mary Barber and co-workers of the Hammersmith Hospital (*Brit. M. J.*, Jan. 2, 1960). An accompanying editorial stated that a series of preventive measures has helped to control these infections. A policy for the use of antibiotics was introduced, to be observed throughout the hospital. Prophylactic use was sharply restricted, the use of penicillin was abandoned except in specified wards, and when antibiotics were used two were given together or one was combined with a sulfonamide. K. Knorr and A. Wallner confined the use of antibiotics in a maternity unit as far as possible to tetracycline and oleandomycin, with the result that the frequency of staphylococcic resistance to some antibiotics decreased by about 50% although resistance to penicillin decreased only from 87 to 73%.

In the larger and more protracted study at Hammersmith Hospital, a similar effect was observed. Among strains isolated from patients, the frequency of penicillin resistance decreased from 74 to 52% and of resistance to both penicillin and tetracycline from 51 to 36%. Strains possessing multiple resistance were responsible for most of the more serious infections which occurred. The authors discussed the question of whether these strains are intrinsically more virulent, but it was difficult to distinguish such an intrinsic property from the consequences of simple resistance to therapy. However, the morbidity and mortality from these infections decreased during this period. There was also a diminution in the frequency of penicillin-resistant strains in nurses who were carriers. The results might have been better if repeated importation of resistant strains in patients transferred from other hospitals had not occurred.

Iron Deficiency Anemia.—Cox and co-workers reported subnormal serum concentrations of vitamin B_{12} in a number of patients with iron-deficiency anemia (*Lancet* 2:998, 1959). The marrow showed no evidence of megaloblastic erythropoiesis, and the hematological findings did not differ significantly from those of a group of patients with iron deficiency and normal serum vitamin B_{12} levels. All patients showed a return to a normal blood picture, including a normal serum vitamin B_{12} level, after treatment with iron only. Hitherto it was believed that B_{12} deficiency, as indicated by low serum levels is always associated with marrow changes. The observations of the authors indicate that this is not so. The finding of subnormal serum vitamin B_{12} levels in patients with iron-deficiency normoblastic anemia caused by repeated acute blood loss suggests that either the serum vitamin B_{12} level is not an accurate measure of the body stores or that a deficiency of vitamin B_{12} can occur without either neurological or hematopoietic abnormalities. In the patients in the present study the slow return of the serum vitamin B_{12} to normal, after hematological remission with iron therapy, suggests that a failure of absorption was corrected. This view was supported by the more rapid return of the serum vitamin B_{12} level to normal in patients with anemia due to blood loss, probably as a result of mobilization of vitamin B_{12} from the tissues.

Sedimentation Rate of Stored Blood.—Drs. Melville and Rifkind of Glasgow (*Brit. M. J.*, Jan. 9, 1960) reported that the need to set up sedimentation rate estimations immediately after withdrawal of blood samples was obviated by taking the blood into the anticoagulant, edathamil. When this was used there was no significant retardation of the sedimentation rate up to six hours after the blood was taken. It did not matter whether the blood stood undisturbed or was mixed at intervals, provided it was thoroughly mixed before the estimation was made. Storage for longer periods at room temperature was often accompanied by marked retardation of the sedimentation rate. Storage of edathamil-treated blood in the refrigerator for 24 hours did not affect the sedimentation rate, but storage for 48 hours was usually attended by marked slowing of the rate. It was recommended that edathamil-treated blood not be used for sedimentation rate estimations if it has been kept in the refrigerator longer than 24 hours.

CORRESPONDENCE

THE DOCTOR ABROAD

To the Editor:—When a physician plans a trip to some foreign country, he will miss a great deal if he overlooks the fact that he is a doctor. The purpose of this letter is to suggest that the physician use some of his vacation time for international good will, for the exchange of ideas with colleagues in other countries, and for the personal satisfaction of being a humanitarian. We may not turn out to be as selfless and effective as Albert Schweitzer, but we should carry out some of the traditions of the Hippocratic oath. I believe that members of the medical profession can create more international good will and help more to lessen international and interracial tension than all the millions of dollars our paternalistic government is pouring into dams, factories, and good-will missions. The reasons are self-evident. Official government missions, with the best of intentions and the most altruistic of motives, are often regarded with suspicion. This does not mean that we as a nation should stop giving and helping; on the contrary, we should do more and more, even if our motives are misunderstood. Some good must come of it. However, we as physicians can do a great deal on a personal and unofficial basis.

When a doctor visits a foreign country and seeks out a hospital, a local physician, a local health station, or whatever the unit of medical care happens to be, he may be performing a service for the United States. If he introduces himself and states that he has come to learn, to observe, to exchange ideas, and to be of some help if possible, he will be welcomed with open arms, with courtesy, and with respect. It is not only the personal contribution that counts but the desire to be friendly, to show interest, and to offer something of himself. I have seen, heard, and shared many experiences of this type and I believe that the physician who has not has missed some of the most rewarding experiences of his lifetime.

You may find out, to your surprise, that you learn more than you teach. You may see examples of diseases which are common locally and are treated successfully with local remedies, whereas these same disorders are rare in your practice or unresponsive to the measures you employ. You may make friends with whom to correspond over the years and whose friendship makes an average trip a fascinating vacation. You may end up by sending your colleagues medical supplies needed locally, hard-to-get journals, equipment easy for you but impossible for them to obtain, or you may merely continue a relationship based on common interests, a mutual desire to help the sick, and a sincere friendship. This same feeling may permeate the other people in the community, namely, of that nice American doctor who came in friendship and only wanted to be helpful.

In the summer of 1958 I visited Italy as an official representative of the United States Committee of the World Medical Association. I enjoyed several meetings with the president of the medical society of Rome, Dr. Carlo Prandi, and with other physicians. These conferences were in the nature of preliminary explorations in order to develop spheres of mutual understanding and to obtain information about problems of significance on both sides of the Atlantic. My primary interest in dermatology drew me to Dr. Ugo Granelli, one of the leaders of Italian dermatology and the director of the Ospedale San Gallicano in Rome. This hospital was built in the early 18th century and it is one of the largest institutions in Italy devoted entirely to the treatment of diseases of the skin. Despite the antiquity of the building, it is well equipped for the modern dermatological care of about 350 inpatients and many more clinic patients. Dr. Granelli has a large and competent staff of dermatologists and specialists in related fields. The institution services one of the largest and poorest districts of the oldest part of Rome, the Trastavere. During several of my visits with Dr. Granelli, it was my good fortune to examine patients with ordinary or rare skin diseases and to exchange information about recent developments in the field. Certain procedures and techniques were relatively new to both Italian and American dermatology, and I was asked many questions about skin planing or dermabrasion, with which they had then had little personal experience. As a result, I promised to equip their clinic with the items necessary for this procedure and to return the following summer to demonstrate the somewhat complicated technique.

I returned in the summer of 1959, after having shipped the necessary equipment to the hospital in the early months of that year. It is difficult to describe the pleasure of this reunion and the affection with which I was greeted by my many medical friends in Italy. A special surgical room had been set up in the Ospedale San Gallicano and many of the staff were on hand to observe several demonstrations of the new technique. I was gratified by the interest of the doctors and especially by the presence of the dean of the medical profession in Italy, Dr. Raffaele Chiarolanza, the president of the national federation of the medical societies of Italy.

If this letter has served to demonstrate some of the issues raised in its opening paragraphs, it will have served its purpose. Remember that it is not necessary to travel on an official mission in order to show interest in a country from a medical standpoint. It is only essential that you make an effort to show friendliness and human interest as a physician and include with it an offer of your own services as a humanitarian. You will never regret it.

Howard T. Behrman
Associate Professor and
Director of Dermatological Research
New York Medical College
New York.

HYPERSENSITIVITY TO IMMUNE SERUM GLOBULIN

To the Editor:—The clinical note in The Journal, Sept. 26, 1959, page 415, is a case report entitled "Hypersensitivity to Immune Serum Globulin." The publication of this seems unfortunate to me, since both diagnosis and treatment are open to question. The inaccuracies which it contains could lead to disaster in circumstances of a similar nature. The concept of spontaneous hypersensitivity to human immune serum globulin is hardly borne out by any of the evidence or comments printed. The fact that both parents had a strong allergic history scarcely gives any additional credibility to this diagnosis, in a 15-week-old child who has yet to manifest one symptom of an allergic nature despite the fact that it has met and apparently overcome successfully innumerable antigens.

Even the comments of the consultant which are included contain rather misleading statements; e. g., speaking of the possibility of allergy, "The mechanism is of some interest. The baby was only 15 weeks old at the time of the injection. This might mean that this baby still possessed atopic reagins from its mother." No one, not even the most enthusiastic supporter of a hereditary concept in allergy, has ever stated or shown that atopic reagins are transmitted from the mother through the placenta to the infant (Kuhns: *Am. J. Med.* 20:251 [Feb.] 1956).

The second suggestion, that of a vasomotor reaction, seems to me the more likely diagnosis. This has probably, in the past, been frequently accepted or misconstrued as an immediate anaphylactic type of reaction. I have seen a state of acute syncope, which resulted also in the onset of a grand mal seizure with complete evacuation of the bladder contents, frothing at the mouth, and holding of the breath, after a skin test in a 14-year-old girl. By the use of hypnotic suggestion, removing sensation from the arm that testing was performed in, this could be completely obviated or made to recur at will. Should this be called an anaphylactic reaction of an allergic nature?

Apparently this 15-week-old boy, who had never had an injection before, resented the intrusion of a 20-gauge needle into his buttock in such a manner that a deep, firm indurated area, 2 in. in diameter, remained for several days thereafter. This suggests a local hematoma.

As for the treatment described, it appears to me that most of what occurred to the child afterward was the result of overmedication, beginning with 1 cc. of epinephrine and its subsequent repetition, and of the other drugs used. The ferocity of the therapy may reflect the physician's acute distress. This apparently was the infant's first experience with an injection, because a statement is made that at the age of 7 months no other injections had been given. One would wonder why immunizations of the usual type were not begun earlier in a 15-week-old boy who appeared to be thriving.

This case report aptly ends with the statement that there are no other reported cases of sensitivity to gamma globulin, although perhaps 40 million cc. has been distributed and used. It fails to state also that many of these had been used in allergic children. Articles such as this should be more carefully screened, with an eye to their implications both in diagnosis and in treatment.

Edward Pickert, M.D.
679 Irvington Ave.
Newark 6.

BREAST CANCER

To the Editor:—In The Journal, Oct. 31, 1959, two references to simple mastectomy for cancer require further comment. I refer to the article, "Survival Rate of Patients with Breast Cancer in a Small Community" (page 1180), and the filler on page 1220 entitled "Simple or Radical Mastectomy?" In the article, table 1 indicates that McWhirter's five-year operative survival rate was 58%. This is a pernicious figure which, in my estimation, should not be circulated without a full and complete analysis showing what McWhirter meant by "operable" and what virtually the rest of the surgical world means by "operable." McWhirter limited his "operable" group to only 56% of patients coming to him for treatment, whereas the Mayo Clinic finds 84% operable. (Berkson and others: *Proc. Staff Meet. Mayo Clin.* 32:645 [Nov. 13] 1957.)

The general findings in the treated patients reveal that McWhirter had a 48.1% and the Mayo Clinic a 59.3% five-year survival rate, based on treatment rendered in the period 1941-1947 by both. While the Mayo Clinic has shown consistent improvement over the years in the rate of five-year survival (65.1% of the operable patients in the period 1950-1954), we do not know whether McWhirter's figures bettered or worsened with the trial of time. Furthermore, while McWhirter has not revealed his 10-year survival figures, there is reason to suspect that radiation may not kill but may merely retard the growth of cancer cells in axillary nodes. Does axillary radiation, then, not cure but merely postpone regional recurrence? In contrast, of all patients treated in the most recent group at the Mayo Clinic, 45.9% survived death from all causes for 10 or more years after operation, while those with axillary metastases had a 29.5% 10-year survival rate.

The extract from Dr. Case's article on page 1220 reflects only therapeutic nihilism not substantiated by fact. He reasons as follows: Since cancer of the breast has so many pathways of spread, why attack only one, the axilla? We as physicians deal not *primarily in philosophy*, but *in facts*. Where is his evidence? The end-result of the controversy between proponents of simple and radical mastectomy is not simply a didactic one. The lives of many women hang on the decision made by their physicians. The responsibility of publishing full and complete findings rests with the editors of the various journals. The references cited in the two articles were misleading, potentially harmful, and undeserving of publication without comment.

John Sonneland, M.D.
104 W. Fifth Ave.
Spokane 4, Wash.

REACTIONS TO POLIOMYELITIS VACCINE

To the Editor:—The article "Reactions to Poliomyelitis Vaccine" by Christensen in The Journal, Oct. 17, 1959, page 869, implies certain things about reactions to the penicillin contained in poliomyelitis vaccine which are not necessarily true. The statements that, "It seems likely that most of the severe reactions would have been reported," and that Eli Lilly & Co. has had only 284 complaints after 184 million ml. of the vaccine was distributed are illogical. Even if all reactions known were reported to the company, as noted by the A. M. A. Council on Drugs in discussing the similar problem of trace amounts of penicillin in milk (*J. A. M. A.* 171:49 [Sept. 5] 1959), such penicillin reactions "have gone unreported and unrecognized." I had a paper on penicillin reactions to poliomyelitis vaccine in The Journal, Aug. 9, 1958, page 1807, but I did not report to the company, although the first case reported in the paper was an allergic reaction to penicillin in Lilly vaccine.

The author's assumption that the *incidence* of reactions is one to 1,200,000 doses is at variance even with the sources quoted in his bibliography. Statistics in these vary from "allergic reactions in 110 out of 4,340 patients" to "major reactions in 1 out of 25,000 persons."

While his statement that "antibiotics cannot be omitted from the manufacturing process of poliomyelitis vaccine" is true, since May 26, 1955, other antibiotics have been used instead of penicillin. Wyeth vaccine, to which polymyxin B is added, is virtually penicillin free (less than 0.001 IU per milliliter).

It was pointed out by the A. M. A. Council on Drugs that "Antibiotics such as bacitracin, neomycin, polymyxin B, and the tetracyclines . . . do not pose a hazard to health. . . . On the other hand, even in small amounts, . . . penicillin, which is highly antigenic, is capable of causing allergic reactions in highly sensitive individuals." If the author is going to give a bibliography, it seems to me that he might include reference to such comments. In the United States we are now reaping the whirlwind of our profligate use of penicillin for the last 15 years.

Murray C. Zimmerman, M.D.
301 E. Hadley St.
Whittier, Calif.

This letter was referred to the author of the original article, whose reply follows.

To the Editor: My experience, the experience of my practicing physician friends, and the records at Eli Lilly and Company strongly suggest that allergic reactions to the penicillin in poliomyelitis vaccine are extremely infrequent. It was believed important to express this view in print because the contrary one has been published by certain authors, including Zimmerman (*J. A. M. A.* 167:1807 [Aug. 9] 1958).

Zimmerman is right when he says that, from the data available to the company, the incidence of reactions cannot be computed, and this point was stressed in the summary of my article: "Because of incomplete reporting, the data do not allow an estimate of the incidence of reactions." It may also be said that the data presented in Zimmerman's article *do not allow an estimate* of the incidence of reactions, yet he states that "six cases from private practice between May and November, 1957, indicate that penicillin reactions to poliomyelitis vaccine are *relatively* common."

Federal regulations do permit the use of antibiotics other than penicillin in the manufacture of poliomyelitis vaccine, but in the past all manufacturers used penicillin, and it is my understanding that they all continue to use penicillin, at least in *the initial tissue-culture phase* of manufacture. This last statement may no longer be true, because not all manufacturers have recently published details about this aspect of their production methods. If penicillin is used in the early tissue-culture stage (before the addition of seed virus), it does not have to be declared on the label of the product. Nevertheless, an unknown number of penicillin molecules could remain in the final product, but, even with the method of production which we use, most lots of the final product contain less than 0.001 unit of penicillin per milliliter (Thompson and others: *Proc. Soc. Exper. Biol. & Med.* 102:377 [Nov.]

1959). Although this amount of penicillin may represent a hazard to a few highly sensitive persons, the available data suggest that such persons are encountered extremely infrequently. I have not heard of a death due to anaphylaxis after the administration of poliomyelitis vaccine.

From a medical viewpoint, there has been good reason to be reluctant about changing to other antibiotics. During the field trials of 1954 (Francis and others: *Am. J. Pub. Health* 45:2 [May, part 2] 1955) allergic symptoms were recorded less often n children given vaccine than in those who were nerely observed (given neither vaccine nor penicillin-containing placebos). This suggests that the ncidence of allergic reactions reputedly due to poliomyelitis vaccine may approximate the prevaence of allergic symptoms occurring from multiple causes in large population groups at any one time. Under these circumstances, there is no reason to expect that a change in antibiotic would significanty alter the incidence or severity of allergic reactions.

Furthermore, many antibiotics are toxic to cells n tissue culture and will render the cells less able o support the growth of virus. If a "toxic" antibiotic were used in the vaccine, the antibiotic could damage the cells of tissue cultures used for safety testing, and, thus, live virus might not be detected n the finished vaccine. Until we at Eli Lilly and Company can complete our evaluation of all ramications of a change in our production methods, we are unwilling to make any change in the procss that might, even in theory, have an adverse earing on safety. Because this company has been he major producer of poliomyelitis vaccine, it has felt keenly the responsibility to avoid, if possible, ny interruption in supply and therefore has been onstrained not to tamper prematurely with a prouction process which we know results in a safe roduct.

C. N. Christensen, M.D.
Medical Division
Eli Lilly and Company
Indianapolis.

THE CHRONIC ALCOHOLIC

To the Editor:—In The Journal, Dec. 26, 1959, page 299, there is an excellent article on the chronic lcoholic. Doctors Pannill and Smith pointed out he importance of providing these persons with eneral hospital care during the acute stages of heir disease and emphasized the importance of he family physician in their future care. They id not, however, emphasize one important point, which is a basic tenet of Alcoholics Anonymous. The chronic alcoholic cannot take even one drink. Some physicians and members of Alcoholics Anonymous realize this, but all physicians should be aware that chronic alcoholics should not drink any alcohol, nor should they take medicaments containing alcohol such as elixirs or tonics.

The authors mention the sober state which, in chronic alcoholism, depends on the patient's taking no alcohol whatsoever. While some chronic alcoholics can drink in moderation for a few weeks or even months, they usually lose control and revert to their former condition. Alcoholism is a disease, the cause of which is unknown, but it seems that chronic alcoholics are in some way sensitive to alcohol. It should be strongly emphasized to these patients that it is no more possible for them to drink alcohol than it is possible for a patient who is sensitive to penicillin to take that drug.

Harry F. Klinefelter Jr., M.D.
1101 N. Calvert St.
Baltimore 2.

YOUNG TURKS

To the Editor:—Your editorial on "Young Turks—Old Turks" in The Journal, Dec. 12, 1959, page 2102, brings cheer to all those interested in clinical investigation, and for this we can be grateful. A couple of historical points can be questioned, however. I think it was to the Society for Experimental Biology and Medicine, and not the ASCI, that the term "Meltzer Verein" was applied—Meltzer was a founder of both. Also, I do not think the "Young Turks" revolted against the "Old." In fact, the latter encouraged the formation of the former. The term "Young Turks" was applied because at the time the newspapers were full of the so-called Young Turk movement in Turkey, and the name got to be used very loosely.

James Howard Means, M.D.
60 Mount Vernon St.
Boston 8.

Thanks for the corrections.—Ed.

INTERMEDIUM

To the Editor—The title of an editorial in The Journal, Jan. 30, page 456, contains the word "intermedium." I am unable to find this word in my dictionary.

M. J.
New Jersey.

In my dictionary, published only a few days ago (1960), there are eight lines devoted to "intermedium." Zoologically speaking, this is "the bone or cartilage situated between the radiale and ulnare in the carpus. . . ." The definition applicable to the term in the title refers to an intervening agent or instrument, similar to the legal use of "instrument" as a document. Either you should procure a larger dictionary, or I should be content with a smaller one.—Ed.

MEDICAL FILM REVIEWS

Transperitoneal Bilateral Lymphadenectomy for Testis Tumor: 16 mm., color, sound, showing time 11 minutes. Produced in 1958 by and procurable on loan from Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington 12, D. C.

After a discussion of various retroperitoneal approaches to this operation, the midline transperitoneal incision is demonstrated. The peritoneum is opened and organs and nodes are palpated. The transverse colon and small intestine are exteriorized and packed. Dissection is illustrated and described in detail and the nodes and spermatic vessels are removed. Closure and sutures are shown. A postoperative view of the incision shows no evidence of herniation or limitation of motion. Interest would have been added to the film if a discussion of the pathological findings on the dissected nodes had been included. This film makes good use of schematic drawings to introduce specifics of the following operation and to describe briefly the operative procedures used in surgical correction of testis tumors to this time. Close-up views during the operation permit good visualization of the procedure. The photographic quality is good except for the footage used in the introduction. It is primarily of interest to urologists and general surgeons and also recommended for residents and interns.

A New Transparent Plastic Surgical Drape: 16 mm., color, sound, showing time 17 minutes. Prepared in 1959 by William G. Pace, M.D., R. M. Zollinger, M.D., and Marjorie Reed, R.N., Columbus, Ohio. Procurable on loan from Aeroplast Corporation, 420 Dellrose Ave., Dayton 3, Ohio.

This film demonstrates and describes the use of this new type of drape for operative incisions of the abdomen, chest, extremities, and neck. The descriptions of the use of the material and the spray-on adhesive required for its application are adequate and understandable. The film illustrates and the narrator describes the various advantages obtained by the use of this material in operative surgery. One possible advantage that is not mentioned is its use to collect blood from the operative field in infants or very small children during open-heart or other types of surgery where, of necessity, a fair amount of blood loss is unavoidable. This would enable more accurate measurement and, therefore, replacement of blood loss in these patients. It would appear that this new type of drape will receive increasing usage as knowledge of its availability is increased. The exposure, illumination, and color are good to excellent at all times. The film will be of interest to interns, residents, and general surgeons.

Physical Diagnosis of the Ear, Nose and Throat: 16 mm., color, sound, showing time 28 minutes. Prepared in 1959 by William H. Saunders, M.D., Columbus, Ohio. Procurable on rental ($6) or purchase ($240.) from the Ohio State University, Department of Photography, Motion Picture Division, 1885 Neil Ave., Columbus 10.

This film shows exacting details of physical examinations of the ear, nose, and throat. There are three sections: first, the ear; second, the nose and paranasal sinuses; and third, the oral cavity, nasopharynx, larynx, and neck. At the end of the film is a short recapitulation. The film explains specific points and shows exactly how the various areas are examined. This film demonstrates procedures very well and the instrumentarium most frequently used in the examination of the ear, nose, and throat. It gives the student a view of the area examined. In general, the photography is excellent and the narration is good. Although areas and structures under examination are visible to the viewer, use of animated diagrams could have been employed to explain more fully the principles involved. Some schools may prefer minor variations in technique; however, this film will serve to give the necessary basic instruction. It is highly recommended for sophomore and junior medical students.

The Diagnosis and Treatment of Depressions in General Practice: 16 mm., black and white, sound, showing time 21 minutes. Prepared by S. Bernard Wortis, M.D., New York. Produced in 1959 by Medical Dynamics Inc., New York, for and procurable on loan from Wallace Laboratories, New Brunswick, N. J.

The author presents a clinical lecture on psychiatric depressive states interspersed with scenes purporting to show patients with various forms of these disorders. The validity of the differential diagnostic classifications may be questioned, and psychiatrists will readily detect that the rehearsed histrionics of the subjects used cannot accurately reproduce the variously strained, retarded, appealing, quasi-self-deprecating, demanding, or desperate sufferings of the truly melancholic patient. However, these minor defects do not seriously impair the usefulness of this film in reminding physicians in all specialties of the incidence and importance of depressive reactions in patients they may encounter in their daily practice. The author also furnishes good advice as to preventative measures and supplies excellent leads regarding balanced treatment by environmental support, drug administration, psychotherapy, or referral in appropriate cases. The photography and narration are good. The points are well made and the story moves on quickly. The film is recommended for teaching residents, medical students, and medical practitioners.

The Faces of Depression: A Phenomenological Approach to the Depressive Syndrome: 16 mm., black and white, sound, showing time 28 minutes. Prepared by Hans E. Lehmann, M.D., Montreal. Produced in 1959 by Robert Anderson Associates Ltd., Ottawa, for and procurable on loan from Geigy Pharmaceuticals, Professional Service Department, P. O. Box 430, Yonkers, New York.

This film presents a series of illustrations of depressed patients before, during, and after various forms of therapy. Among its merits are the following: each scene is manifestly genuine, there is no insistence on rigid classification, the author and his associates present a sympathetic mode of interviewing and a discerning commentary, and the closing scenes properly emphasize an optimistic approach to prognosis and treatment. The film may be used for psychiatric teaching, or, with appropriate explanations, for presentation to intelligent lay audiences, although here the possibility of someone recognizing the undisguised patients, though remote, would be a deterrent. The photographic quality is good. This film is recommended to general practitioners, psychiatrists, residents, and psychologists.

Vaginal Construction for Agenesis: 16 mm., color, sound, showing time 17 minutes. Produced in 1959 by and procurable on loan from Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington 12, D. C.

The purpose of this film is to describe a technique by which a functional vagina may be constructed in a patient who has congenital absence of the vagina and uterus. It shows the preoperative studies, the plan of surgery, and the immediate and ultimate surgical result. The operation is straightforward and the technique is excellent. However, the graft is cut so thick that one year later the girl still has a noticeable scar on the inner aspect of her left thigh. The assumption can be made that a complete diagnosis of the patient's condition justified this operation. From the standpoint of technique of manufacture of an artificial vagina this film is excellent. The color is good and the sound is fair, but the photography does not have quite sufficient depth of field for adequate vaginal visualization. The film would be of primary interest to gynecologists and general surgeons and could be recommended for residents and interns.

NEW FILMS ADDED TO A. M. A. MOTION PICTURE LIBRARY

Bronchocinematography: 16 mm., black and white, sound, showing time 15 minutes. Prepared by Shogo Awataguchi, Sendai, Japan. Procurable on loan (service charge $3) from Motion Picture Library, American Medical Association, 535 N. Dearborn St., Chicago 10.

Fluorocinematography has been made a practical and valuable medical tool by the development of the image intensifier. Through its use, fluoroscopic images may be preserved for record and teaching. These points are particularly well illustrated in this film. It begins with an illustrated discussion of the instrumentarium and techniques of fluorocinematography. After this, the contrast media, equipment, and technique of bronchography are described and shown. The principle portion of the film, however, consists of bronchographic demonstrations, the recorded fluoroscopic image following the filling of various types of physiological and pathological bronchial patterns. Bronchial motility is well shown. Tubercular and bronchiectatic cavities are illustrated, and the effect of bronchial stenoses on the flow of the oily medium is shown. This type of film will certainly be improved technically as new equipment is developed. Yet the basic concepts of bronchial physiology and pathology are included. For this reason, it is of value to medical students as well as specialists in the fields of radiology and diseases of the chest.

Radiation: Physician and Patient: 16 mm., color, sound, showing time 45 minutes. Presented by the American College of Radiology in cooperation with the United States Public Health Service. Supported by a grant from the Rockefeller Foundation. Produced in 1959 by Medical Radio and Television Institute Productions, New York. Procurable on loan from Motion Picture Library, American Medical Association, 535 N. Dearborn St., Chicago 10.

This film brings together some of the nation's foremost authorities in radiation cell damage, genetics, carcinogenesis, and physics, with some well-known physicians shown in the process of referring their patients for x-ray examinations and consulting with the radiologist in a highly effective manner. The excellent photography of these authorities in their offices and laboratory environments is priceless as a record; however, at times there is too much emphasis on the individual person, which distracts from the information being conveyed. The concern and attitude of several referring physicians toward their patients present, answer, and clarify the major radiation questions of the day. Since the patients are chosen from such critical areas as pediatrics, orthopedics, and obstetrics, everyday problems are faced and analyzed. The presentation has a relaxed air which makes the patient consultations seem natural, and there is little hysteria. Anyone who uses fluoroscopy and who sees nothing wrong with the opening sequences should be compelled to see the whole film. The closing sequences will deliver a message to such a viewer which will either impress him enough to change his ways or encourage him to give up fluoroscopy. This is an important film for the nation's practicing physicians, medical teachers, and medical radiation research workers.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

The Liver in Wilson's Disease. I. H. Scheinberg and I. Sternlieb. Gastroenterology 37:550-564 (Nov.) 1959 [Baltimore].

Confusion about the role of the liver in hepatolenticular degeneration (Wilson's disease) induced the authors to review the role of the liver in the light of recent investigations. On the basis of 74 published reports, they conclude that hepatolenticular degeneration is the result of an inherited defect in protein synthesis, which can be recognized by a deficiency of the plasma copper-protein, ceruloplasmin, and which is associated with disturbances of copper metabolism. A continued small positive copper balance apparently results in the deposition of excessive amounts of copper in the liver, brain, and other organs. Large amounts of copper can be present in the liver for a year, and probably considerably longer, without causing significant pathological changes or symptoms. Eventually, however, the liver seems to react to the deposited copper with degeneration and necrosis, which finally result in a typical clinical and pathological picture of postnecrotic cirrhosis.

Specific treatment of this hereditary hepatic disease can be directed only toward the environmental factor which probably makes it manifest—copper. A regimen may be used to prevent absorption and promote excretion of this metal. The results of such therapy in patients with already diseased livers have not been encouraging, although marked improvement in neurological symptomatology has been effected. Treatment of the postnecrotic cirrhosis itself differs little from the usual treatment of this condition. It is possible to detect asymptomatic and healthy children who will develop this disease. Treatment of such persons to prevent further copper deposition and to remove copper already deposited may be expected to prevent or delay onset of the disease.

Primary Biliary Cirrhosis (Chronic Intrahepatic Obstructive Jaundice). S. Sherlock. Gastroenterology 37:574-586 (Nov.) 1959 [Baltimore].

Sherlock points out that the association of the clinical picture of prolonged obstructive jaundice (cholestasis) without mechanical obstruction to major bile ducts is well known, having been described in 1851 by Addison and Gull and later by Hanot, Thannhauser, and Magendantz and many others. In 1950 Ahrens and co-workers reviewed the literature on the condition and described personally observed cases under the term "primary biliary cirrhosis," which Sherlock regards as an ambiguous term. The most important feature of this lesion is the disturbance of the zonal architecture of the liver by regeneration, so that each nodule is divided by short, wide venous channels (internal Eck fistulas). This is certainly not true of primary biliary cirrhosis, in which nodular regeneration is inconspicuous and disruption of the essential architecture is a very late feature. "Chronic intrahepatic obstructive jaundice" is a better term.

The author presents observations on 42 patients (36 women and 6 men, mostly middle aged or elderly), who were followed up between 1944 and 1959. The onset of the disorder was insidious, usually with pruritus coincident with, or followed by, jaundice and skin pigmentation. The liver was always enlarged; the spleen was palpable in 80% of the patients. Depth of jaundice was variable. In the most deeply jaundiced patients hepatocellular failure developed the soonest. Certain diagnosis is usually impossible without laparotomy, preferably with direct operative or postoperative cholangiography. The mean duration of the disease in 23 fatal cases was 5 years, 5 months. Hepatocellular failure was the commonest cause of death (15 patients). Xanthomas were seen in 20 patients, all of whom had high serum cholesterol values. Xanthelasma was noted in 6 patients, often with virtually normal serum cholesterol levels. Steatorrhea was in proportion to the serum bilirubin value. Bone thinning was noted in 21 of 34 patients investigated. Pain was relieved by vitamin D injections and oral administration of calcium, but bone thinning progressed.

Gastrointestinal hemorrhage occurred in 16 patients (in 9 from a peptic ulcer and in 7 from esophageal varices). In all, 13 patients had a peptic ulcer. Portal blood pressure was usually raised, but clinically significant portal hypertension was rare. The onset of hepatocellular failure was marked by deep-

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The place of publication of the periodical appears in brackets preceding each abstract.

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ening jaundice and falling serum albumin level with peripheral edema. Ascites was rare and terminal. Disappearance of pruritus and xanthomas and a fall in serum cholesterol and alkaline phosphatase levels foretold the end. Treatment was symptomatic. Intractable pruritus was relieved by methyltestosterone or norethandrolone, but jaundice deepened. Blood bile acid levels did not fall with relief of pruritus. Fat-soluble vitamins were given by injection, and calcium was given orally. Corticosteroid therapy proved ineffective. The etiology of the condition is obscure.

Pathogenesis of Myocardial Infarct. K. F. Feiks. Wien. Ztschr. inn. Med. 40:345-355 (Sept.) 1959 (In German) [Vienna].

The author analyzed the records of 513 patients who were admitted to a Vienna hospital on account f myocardial infarction between 1953 and 1958. There were 360 men and 153 women. The infarct vas new and extensive in 470 of the patients who vere admitted with severe symptoms during the irst 2 days of their illness. In the remaining 43 atients the infarct had been in existence for some ime, or was small. The mortality averaged 41% mong men and 49% among women. The death ate was especially high among those in whom he infarct involved the ventricular septum and n whom the electrocardiographic record indicated low healing. The mortality was also higher among atients with high blood sugar or leukocyte values; special sympathetic reactivity, rather than unusully large infarcts, seemed to be the cause of these leaths.

Autopsy was performed on all of the 224 patients vho died as the result of their infarcts. In 62 cases 28%) no thrombus could be found. While the cornary arteries of the large majority of the patients vithout thrombus showed severe atherosclerotic hanges, there were some in whom the coronary rteries were practically normal, and yet the myoardium showed large new areas of myomalacia. n this connection the author cites literature reports hich indicate that functional circulatory disturbnces may lead to the formation of areas of myoalacia. Furthermore, atherosclerotic vessels may e more sensitive to oxygen deficiency, and this reater sensitivity may be further increased by pasm.

In studying the case histories, the author oberved a high incidence of occupations of a sendenary nature. Many patients had a history of ypertension or of diabetes, but as regards cigarette moking there was no noticeable difference beween the patients with infarcts and the control roup. Few of the patients with infarcts (less than alf as many as the controls) were in the habit of aking small quantities of alcohol with their meals, ut many drank large quantities of coffee. Complete abstinence from alcohol was relatively frequent among infarct patients. Many had a second job, in addition to their main occupation. The author feels that the assumed vasodilator effects of the small amounts of alcohol are probably less important than the psychological differences between the infarct patients and controls, patients with infarcts being, on the whole, more tense than the controls. In the majority of patients the history revealed a preinfarction stage of subjective symptoms, but in about one-fourth of them the myocardial infarct occurred without any precursory symptoms of stenocardia. The patients reviewed in this group included 110 in whom the infarct was the second one, and 18 who had a third infarct. Of those with a second infarct, 58 died; thus, patients with a second infarct had a higher mortality rate. The interval between the first and second infarcts was, in most instances, less than 2 years.

The Use of a Vasopressor Agent as a Diagnostic Aid in Auscultation. L. Crevasse. Am. Heart J. 58:821-826 (Dec.) 1959 [St. Louis].

A vasopressor agent has been found useful in converting the late systolic or atypical murmur of patent ductus to the typical continuous murmur. Rapid changes in cardiac output and increases in aortic pressure can be useful in clarifying or intensifying certain murmurs. The studies aimed to determine the clinical usefulness of rapid changes in cardiac output and aortic pressure on the intensity and graphic form of the common congenital and acquired heart lesions. The following cases were included in this study: aortic stenosis (5); pulmonic stenosis (5); tetralogy of Fallot with Blalock shunt (2); atrial septal defect (4); aortic insufficiency (6); mitral stenosis (3); mitral stenosis and insufficiency (4); mitral regurgitation (8); ventricular septal defect with and without pulmonary hypertension (6); pulmonic insufficiency secondary to atrial and ventricular septal defects (5); and functional or contact murmurs (8). The changes in intensity and graphic form were recorded by a Sanborn Twin-Beam phonocardiogram before and during the height of the pressor response after the intravenous administration of 15 to 30 mg. of mephentermine (Wyamine) sulfate. This amine increases aortic pressure by increasing myocardial contractility, while exerting little influence on peripheral arteriolar resistance.

The author describes observations and graphs are reproduced which show how the equivocal or atypical murmur of mitral insufficiency becomes characteristic after the administration of Wyamine. The following points are stressed: 1. Wyamine will accentuate and bring out the graphic characteristi of the murmur of mitral insufficiency in st [illegible] in which the murmur is equivocal or aty [illegible] Increases in aortic pressure will striking [illegible] the intensity and duration of aortic insufficiency and verify its presence in suspected or atypical cases. 3. Pulmonary arterial pressure is altered only slightly in relation to increases in aortic pressure by Wyamine, and the murmur of pulmonic insufficiency remains essentially unchanged, an important feature of differentiation from aortic regurgitation. 4. By raising aortic pressure and widening the aortic-pulmonic pressure gradient, the patency of a Blalock shunt can be determined because the continuous murmur will appear. 5. Functional murmurs or contact sounds are usually unaffected in duration or graphic characteristics. 6. The systolic murmurs of aortic and pulmonic stenosis, and atrial and ventricular septal defects, were all increased in intensity because of the ionotrophic action of Wyamine, and thus provided no useful differential feature.

Study of Intestinal Involvement in Patients with Pulmonary Tuberculosis. A. B. de Pablo. Rev. clín. españ. 74:312-320 (Sept. 15) 1959 (In Spanish) [Madrid].

Two groups of tuberculous patients were studied clinically and roentgenologically in an investigation of the frequency of intestinal involvement in pulmonary tuberculosis. The first group was composed of 400 patients who had not received any streptomycin, animosalicylic acid, or isoniazid. The second group was composed of 250 patients who had previously been treated with at least 2 of these drugs. Three diagnostic categories were established: (1) intestinal tuberculosis, the patient presenting subjective intestinal symptoms together with roentgenologic signs; (2) tuberculous dyspepsia, with subjective intestinal symptoms without roentgenologic confirmation and (3) asymptomatic or silent intestinal tuberculosis, with roentgenologic manifestations but without subjective symptoms.

Roentgenologic signs of intestinal tuberculosis were found in 182 patients (45.5%) of the first group, while subjective symptoms were present in 240 (60%). According to the categories established, 116 patients received a diagnosis of intestinal tuberculosis; 124, a diagnosis of tuberculous dyspepsia; and 15, a diagnosis of asymptomatic or silent intestinal tuberculosis. One hundred forty-five patients (approximately 36%) were free from intestinal involvement. The relationship between pulmonary cavitation and intestinal involvement was studied in 235 patients. Positive roentgenologic signs were found in 159 (85%) of the 188 patients with cavitation and in only 20 (42.5%) of those without cavitation. In the second group of tuberculous patients only 7 (2.8%) presented roentgenologic signs of intestinal tuberculosis. With the exception of a girl who had a primary infection, all presented subjective symptoms, with the clinical picture of chronic tuberculosis and positive sputum culture. The author recommends that every tuberculous patient be subjected to intestinal roentgenologic study. Although the roentgenologic data cannot clarify the etiology of the involvement, they provide valuable elements for the diagnosis and consequent treatment of intestinal complications.

The Marfan Syndrome: A Study of Five Generations in a Kentucky Family. A. M. Gordon. J. Kentucky M. A. 57:1511-1517 (Dec.) 1959 [Louisville].

Marfan's syndrome, which is a rare hereditary disorder of connective tissue, was found in 6 members of a 5-generation Kentucky family. The affected members included the propositus, his father, an uncle, a brother, a cousin, and a niece. The father died at the age of 44 years of "dropsy." The uncle died at the age of 54 years of heart disease. The uncle's daughter died at the age of 32 years of heart disease. Both the father and the uncle were longilineal. The father, the uncle, and the cousin had eye discomfort all their lives.

The propositus, his brother, and the brother's daughter were examined for Marfan's syndrome. All 3 were longilineal. The brother died at the age of 37 years of dissecting aneurysm; he had ectopia lentis and severe pectus excavatum. One of his 3 daughters, aged 14 years, who is still living, has Marfan's syndrome. She is dolichocephalic, has scoliosis of the spine, and has a dislocated lens of one eye. The author believes that this girl and the propositus had the typical Marfan syndrome. The propositus died at the age of 24 years of intractable heart failure. Final anatomic diagnosis after autopsy stated: "Marfan's syndrome, chronic mitral endocarditis with calcification, hypoplasia of the ascending aorta, cardiac hypertrophy and dilatation, bilateral hydrothorax, ascites, chronic passive congestion of liver, pulmonary infarction, pleural adhesion, and phthisis bulbi, right."

North American Blastomycosis. G. L. Baum and J. Schwartz. Am. J. M. Sc. 238:661-684 (Dec.) 1959 [Philadelphia].

The pathogenesis, the clinical picture, and the treatment of North American blastomycosis, a pulmonary disease caused by Blastomyces dermatitidis, which is restricted mostly to the North American continent and which was first described by Gilchrist in 1896, are discussed. Conclusions are drawn from a review of the literature and from the authors' observations of some patients with the disease. Blastomycosis is primarily a chronic indolent active infection which rarely becomes acute and rapidly progressive. The most commonly observed clinical manifestation is the skin lesion; it may appear as a single focus of the disease or may be accompanied by many sister skin lesions in various stages of development. Finally, the skin lesions may be a part of an active disseminated disease, with simultaneous lesions of many internal organs. The one common factor in all variations of the skin manifestations of blastomycosis is that the primary lesion is in the lung and that all the lesions seen, whether localized to the skin or spread throughout the body, are metastatic. Usually, however, no involvement of the gastrointestinal tract is seen in North American blastomycosis. Pulmonary blastomycosis, despite being the primary lesion in all types of blastomycosis, is often clinically silent. There may be no obvious pulmonary focus on clinical or roentgenographic examination, or the roentgenogram may reveal a nondescript scar or thickening. The chronic form of pulmonary blastomycosis is nonspecific in clinical or roentgenographic appearance.

The pathological picture of blastomycosis combines an acute purulent reaction with a chronic granulomatous one in most of the organs in which the disease is observed. In the lung this produces a reaction which, in part, is similar to tuberculosis and the other deep fungous diseases; it also produces a response which is different from any of them. The former is the development of epithelioid-cell granulomas which, except for the presence of the specific organism, are similar in other fungous diseases. The latter is microabscess formation which is commonly found in blastomycosis but not in the other entities. This is seen in all organs and has particular expression in the skin, where the abscesses are visible and serve as sources for diagnostic material, and in the prostate, where abscess formation may lead to urinary obstruction. Caseation necrosis is a reaction not prominent in blastomycosis.

The excellent response of North American blastomycosis to amphotericin B and, in many cases, to stilbamidine and its derivatives has removed the fear of diagnosis of this disease. There is no proof of transmission of this form of blastomycosis from man to man or animal to man. In North America the disease should be suspected in all chronic pulmonary disorders of granulomatous character which are not tuberculous, histoplasmic, or of other mycotic origin. Even when tumor is suspected from roentgenograms, blastomycosis should not be counted out.

The Milk Alkali Syndrome: Case Report of Reversible Hypercalcemia, Alkalosis and Renal Insufficiency. J. F. Crenshaw and L. L. Campbell, J. M. A. Alabama 29:189-193 (Dec.) 1959 [Montgomery].

Although until 1955 only 21 cases of the syndrome of hypercalcemia and renal insufficiency secondary to prolonged excessive milk and absorbable alkali intake had been reported in the literature, more recent reports seem to indicate that this syndrome is more common than is ordinarily suspected. The authors cite the history of a 63-year-old man with a gastric ulcer, who, while ingesting standard amounts of milk and the alkali, calcium carbonate, developed the milk-alkali syndrome, characterized by hypercalcemia, alkalosis, and renal insufficiency without hypercalciuria or hypophosphatemia. There was no evidence of ocular changes or other calcinosis. After a low-calcium diet and withdrawal of the alkali, improvement was rapid and apparently complete. The intake of alkali and milk by this patient did not seem excessive, relative to the usual standards of peptic ulcer therapy. It is believed that the preexistent mild renal impairment exhibited by this patient before being placed on a strict milk-alkali program possibly influenced the development of this syndrome. The diagnosis of hyperparathyroidism was entertained, but appears untenable in view of the disappearance of the chemical abnormalities and the general well-being of the patient.

Primary Aldosteronism: A Review of Medical Literature from 1955 to June, 1958. P. Delorme and J. Genest. Canad. M. A. J. 81:893-902 (Dec. 1) 1959 [Toronto].

The authors analyze the etiological, pathological, clinical, and biochemical aspects, and the postoperative follow-up, of 31 patients with primary aldosteronism, who have been reported since Conn's first description of this condition in 1954. There were 12 men and 19 women, with ages ranging from 11 to 63 years and a peak incidence (16 patients) in the 30-to-45 age group. Pathological adrenal changes were observed in 28 patients, while renal changes were present in 16. The renal conditions were "vacuolar nephropathy" in 8 patients, arteriolar lesions in 10, nonspecific tubular lesions in 3, and pyelonephritis in 3. Arterial hypertension, headache, polyuria, polydipsia, and/or nocturia were the most frequent symptoms at the onset of the disease. Thirteen patients also had muscular weakness when admitted to the hospital. Seven developed tetany during the course of their illness. Hypopotassemia was present in all the patients. Different effects of corticotropin (ACTH) on the urinary excretion of sodium and potassium in patients with aldosteronism have been reported. Dietary changes and administration of specific drugs produce effects which have received different interpretations from different authors.

The characteristic of aldosteronism are summarized. The main cause is adrenal adenoma, although adrenal hyperplasia is more frequent in young patients. Arterial hypertension, polyuria, polydipsia, nocturia, episodes of muscular weakness or of paralysis, and, less often, tetanic crises are the main clinical features. Hypopotassemia, sometimes accompanied by hypernatremia and alkalosis, is a constant finding. Surgery is the only definitive treatment. As arterial hypertension, clinically indistinguishable from essential hypertension, may be the sole manifestation of this condition, plasma potassium determinations should be carried out in every hypertensive patient of any age. The primary importance of recognizing aldosteronism is that it belongs to the small group of causes of hypertension for which a permanent cure may be achieved by operation.

Evaluation of the Pharmacologic and Chemical Tests as an Aid to Diagnosis of Pheochromocytoma. G. M. Roth, E. V. Flock, J. L. Bollman and W. F. Kvale. Angiology 10:426-430 (Dec.) 1959 [Baltimore].

The article deals with the required precautions and encountered difficulties with the pharmacological and chemical tests for the diagnosis of pheochromocytoma. The greatest obstacle to the successful diagnosis of pheochromocytoma is previous medication. The pharmacological test for pheochromocytoma at the Mayo Clinic consists of performing the cold pressor test, followed by administration of either histamine or phentolamine (Regitine) hydrochloride. Histamine stimulates the adrenal tumor to produce the rise in blood pressure and the characteristic attacks. The histamine test is employed in patients with paroxysmal hypertension, and the Regitine test in patients with sustained hypertension. A basal blood pressure, obtained while the patient is lying comfortably for at least half an hour, is important in the interpretation of the results after the administration of histamine or Regitine. Pharmacological tests may yield false-positive results if sedatives, narcotics, and self-medication drugs are not prohibited for at least 48 hours before any test is given. Antihypertensive drugs should be withdrawn for 8 to 10 days. Regitine tests on 3 patients gave negative results while these patients were receiving antihypertensive drugs, but positive results after use of these drugs was discontinued for 8 to 10 days.

In the series studied, administration of histamine also produced increased pressor amines in the plasma and increased catecholamines in the urine. The values for pressor amines in 29 patients with pheochromocytoma ranged from 6.9 to 360 mcg. per liter of plasma. The levels of urinary catecholamines ranged from 42 to 493 mcg. per 100 ml. in 4 patients with pheochromocytoma. Vasoconstrictors, which are used locally for nasal stuffiness, produced false-positive results from chemical tests. The authors carried out 13,117 pharmacological tests on 12,007 patients, 557 tests for pressor amines on 417 patients, and tests for catecholamines on 504 patients during the past 15 years. Seventy-one pheochromocytomas have been diagnosed in 61 patients and have been successfully removed. No untoward effects have developed in connection with the pharmacological tests. The combination of pharmacological and chemical tests offers a high degree of accuracy for the diagnosis of pheochromocytoma.

Treatment of Ulcerative Colitis with Retention Enema of Prednisolone and Phthalylsulfathiazole: Preliminary Report. H. G. Mitchell. Prensa méd. argent. 46:1577-1579 (June 19) 1959. (In Spanish) [Buenos Aires].

Five patients with ulcerative colitis were treated with prednisolone tributylacetate and phthalylsulfathiazole, in the form of retention enema, for periods of 4 to 6 weeks. Two of the patients were men, and 3 were women. Symptoms common in the 5 patients were diarrhea with liquid bloody feces, abdominal pain, and loss of weight. One of the male patients and one of the female (a 26-year-old woman who was pregnant) had undergone temporary transverse colostomy and had obtained temporary relief. The enema mixture was composed of 125 mg. of prednisolone tributylacetate, 16 Gm. of phthalylsulfathiazole, and 2.40 Gm. of carboxymethylcellulose, to which 240 cc. of distilled water was added. Each patient used 30 cc. of this mixture daily, in 60 cc. of lukewarm water, for a retention enema at bedtime. By adding barium to the mixture, it was possible to ascertain radioscopically that the preparation reached the ascending colon in a variable period of time. No toxic or secondary effects were observed. Clinical improvement in 4 patients was confirmed by radiology and endoscopy. The pregnant patient was delivered at term of a healthy fetus. Only a 70-year-old woman, whose condition was critical, failed to respond to the treatment, which was interrupted at the end of 4 weeks.

SURGERY

Results of Decompression Operation for Trigeminal Neuralgia Four Years Plus After Operation. H. J. Svien and J. G. Love. J. Neurosurg. 16:653-655 (Nov.) 1959 [Chicago].

Decompression of the posterior root and gasserian ganglion of the 5th cranial nerve by the extradural procedure (Love's modification of Taarnøhj's original procedure) was performed on 100 patients at the Mayo Clinic between June, 1952, and March, 1954. The authors evaluated the results 4 years or more after the operation in 91 of the 100 patients. Of the 91 patients, 65 did not experience sensory loss after the operation, 15 had experienced subjective sensory loss after the operation, and 11 had experienced objective sensory loss after the operation. Of the 65 patients, 55 (84.6%) had recurrences of trigeminal neuralgia. Ten (66.7%) of the 15 patients in whom subjective sensory loss only was sustained had recurrences. Four (36.4%) of the 11 patients in whom objective sensory loss was present as a result of the operation had recurrences. The significantly better results obtained in the patients who sustained sensory loss because of the operation lend credence to the view that worthwhile results are obtained by means of this procedure only if the nerve is systematically traumatized to a degree sufficient to produce mild to moderate postoperative sensory loss.

Occult Cancer of Breast: Review with Special Attention to Form Primarily Manifested by Metastases to Axillary Nodes. A. Johnsen. Ugesk. læger 121:1681-1686 (Oct. 29) 1959 (In Danish) [Copenhagen].

By occult cancer of the breast the author designates histologically verified cancer of the breast which had not at any time caused manifest symptoms in the mammary gland, and he refers especially to the form primarily manifesting itself by metastases in the axilla, where the enlarged lymph nodes in the axilla are the only signs of the disease. The affected lymph nodes vary in size from small nodules to large adherent masses. If there is a lymph node tumor or other tumor in the axilla, biopsy should be performed, and if pathological examination shows cancer, the patient should be treated as one with cancer of the breast, unless primary tumors elsewhere are known. A woman is never adequately examined for cancer of the breast without thorough palpation of both axillas. The 54 cases of occult cancer of the breast reported in the literature, including the author's case, occurred in 53 women and 1 man, aged from 30 to 71 years. With 3 exceptions, the patients themselves became aware of the axillary tumor, and they came under surgical treatment relatively soon. All 54 were operated on, in practically all cases with radical mastectomy. On the whole, latent cancer of the breast has a somewhat better prognosis than the usual cancer of the mammary gland with axillary metastases.

Stroke Associated with Elongation and Kinking of the Internal Carotid Artery: Report of Three Cases Treated by Segmental Resection of the Carotid Artery. J. K. Quattlebaum Jr., E. T. Upson and R. L. Neville. Ann. Surg. 150:824-832 (Nov.) 1959 [Philadelphia].

As far as the authors could ascertain, all reported instances of obstruction to the carotid circulation have been on the basis of intimal thickening due to atherosclerotic deposits at or near the carotid bifurcation, with or without secondary thrombosis. Their 3 patients, however, had internal carotid occlusion, not secondary to intrinsic narrowing of the lumen, but due to elongation of the vessel of sufficient degree to produce narrowing by way of kinking with associated transient hemiparesis. The patients were a 69-year-old woman and 2 men, aged 75 and 68 years, respectively. One patient was treated by segmental resection of the common carotid artery with end-to-end anastomosis with a good result. The other 2 patients, because of the presence of a partially stenosing atheromatous plaque in the carotid bifurcation, were treated by resection of the carotid bifurcation with end-to-end anastomosis of the common carotid to the internal carotid artery. A fourth case of similar elongation of the carotid artery without symptoms from kinking is reported. It is felt that more cases will be forthcoming as the result of increasing angiographic investigation of the carotid artery currently in vogue. Occlusion times of 13½ minutes of the common carotid artery and of 8½ minutes and 17 minutes of the internal carotid artery were tolerated without serious ill-effects.

In each of these patients the authors were impressed with the flexibility of the arteries. Aside from the localized plaque in the carotid bifurcation in 2 cases, there was no significant sclerosis of the vessels. Obviously the process is one of elongation due to loss of elasticity. As the vessel elongates, it bends on the fixed points at the base of the skull and thoracic inlet. The ending is limited by the resistance of the fascia of the carotid sheath. It was demonstrated on the operating table in these patients that there is a much greater tendency to kinking as the head is turned toward the side of the vessel in question. This has been confirmed by arteriograms. The authors recommend local anesthesia for preliminary exploration and test periods of occlusion before proceeding to general anesthesia, with hypothermia when necessary.

Case of Conn's Syndrome. P. K. M. Barrett, J. R. Rees and D. Marrack. Brit. M. J. 2:1047-1052 (Nov. 21) 1959 [London].

The authors report on a 47-year-old woman with the syndrome of potassium depletion and hypertension due to a benign adrenocortical adenoma, first described by Conn, who named the syndrome "primary aldosteronism." The patient had recurrent attacks of severe muscular weakness and showed pronounced hypopotassemia, but without hypernatremia or alkalosis. Renal function tests showed selective impairment of urinary concentration and acidification. The abnormal renal potassium loss was readily shown, but it was uncertain whether this was due to Conn's syndrome or to potassium-losing nephritis. Renal biopsy showed slight tubular vacuolation only. The absence of pyelonephritic changes in the renal biopsy favored Conn's syndrome, but no increase in urinary aldosterone excretion was found, nor could an adrenal tumor be shown radiologically with the aid of air insufflation.

The electrolyte composition of saliva and feces was normal. The previous history of urinary infection and a culture positive on one occasion for Escherichia coli favored pyelonephritis. The response to high-potassium and low-potassium intakes was studied, and despite continued potassium supply, further potassium depletion occurred, partly explaining the marked increase in extracellular fluid volume. An excessive renal response to sodium restriction was observed. A paradoxical response to stress (such as air insufflation, start of an intercurrent infection, lumbar puncture, renal biopsy) was noted, with increased urinary sodium loss and a less constant potassium diuresis.

Because of the equivocal results, an adrenal exploration was performed on the woman. The left adrenal gland was enlarged, and, on removal, was seen to be largely replaced by a round encapsulated tumor with a striking orange color on section. Microscopic examination of the specimen revealed a benign cortical adenoma, closely resembling those reported in Conn's syndrome. The distinction between Conn's syndrome and potassium-losing nephritis may be very difficult. In patients such as this, even when renal damage is slight, the diagnosis may only be presumptive when biochemical changes other than hypopotassemia are absent, and when no evidence of an adrenal tumor or increased aldosterone production can be shown. These studies are of little value if negative, and in these circumstances the discovery of excessive sodium retention after sodium restriction, and an abnormal electrolyte excretion in response to stress, may be of help. At present the distinction from potassium-losing renal disease may be made only at operation.

Survival of Breast-Cancer Patients in Connecticut, 1935-54. S. J. Cutler, F. Ederer, M. H. Griswold and R. A. Greenberg. J. Nat. Cancer Inst. 23:1137-1156 (Nov.) 1959 [Washington, D. C.].

The authors analyzed the survival of breast-cancer patients in Connecticut over the 20-year period from 1935 to 1954. Attention was given to the stage of the cancer and to the age of the patients at the time of diagnosis and of treatment. The authors used the actuarial method. Survival was measured relative to expected survival in the general population. The 5-year relative survival rate for patients in whom breast cancer was diagnosed during the first 10-year period (1935-1944) was 50%. The mortality among the 5-year survivors was far in excess of that of the general population. The 5-year relative survival rate for patients in whom breast cancer was diagnosed during the second 10-year period (1945-1954) was 56%, but there was no evidence of improvement in the 10-year survival rates. In general, there was little variation in survival rates with regard to age of the patients, except that among those with localized lesions, women ranging in age from 75 to 84 had a somewhat more favorable survival experience than did women under 75 years of age. Among patients with regional spread, women under 35 had a lower survival rate than did older women.

Survival with regard to treatment of breast cancer is about the same in Connecticut as in several well-known treatment centers. Yet the authors feel that this stability of survival rates should not be interpreted as an indication that treatment is futile. From the fact that incidence, mortality, and survival rates have all been stable for a good many years, they infer that future improvement is more likely to result from development of new therapeutic techniques than from further refinement of current methods.

Study of the Cardioplegic Action of Potassium Ion During Normothermia and Hypothermia. A. Kaplan and B. Fisher. Ann. Surg. 150:833-840 (Nov.) 1959 [Philadelphia].

A divergence of opinion exists concerning the clinical use of potassium as a cardioplegic agent during surgical interventions on the heart. The authors began studies on the metabolism of potassium when injected as a cardioplegic agent under various conditions, such as in normothermia, hypothermia, coronary perfusion, and with the pump oxygenator. In this paper they present observations made on normothermic and hypothermic animals concerning the fate of radio potassium (K^{42}) when used for this purpose. Thirty-two mongrel dogs were divided into 3 groups, 1 normothermic and 2 hypothermic groups, one of the latter being given digitalis. Hypothermia was induced by means of a water bath at 2 C (35.6 F). The dog was removed from the bath when its temperature had reached 29 C (84.2 F), but the temperature was allowed to drift down to 25 C (77 F). The further procedure was the same in all 3 groups of dogs. After bilateral thoracotomy, the azygos vein was ligated, and both cavae prepared for venous inflow occlusion. The latter were clamped, as was the aorta, and cardiac arrest was accomplished by the injection of a solution of 25% potassium citrate (2 ml.), isotonic sodium chloride solution (18 ml.), and heparin (0.5 ml.) containing K^{42}. Because of its *half-life* (12½ hours), K^{42} was added to the solution in varying volumes, i. e., 0.02 ml. the day of arrival, 0.06 ml. the second day, and 0.1 ml. the third day. The activity of the solution to be injected was determined by placing the loaded syringe under the scintillation tube just prior to injection. If the activity was found to be reduced, more K^{42} was added to the solution.

From observations on the dogs, the authors conclude that, although large amounts of potassium will compromise the possibility of recovery, in general no uniform relationship exists between the amount of potassium injected and the reversibility of cardioplegia. Simply "washing" out potassium does not necessarily imply that normal rhythm will be resumed, for reversibility does not seem to be entirely related to the concentration of potassium in the myocardium. From its pattern of behavior it would seem that injected potassium is probably distributed into a fast elimination "compartment," from which it is easily removed during resuscitation, and a "compartment" from which there is slower elimination. Normothermic animals with potassium-induced cardiac arrest suffered a 25% mortality, in contrast to one of 70% in the hypothermic dogs. With prior digitalization of the hypothermic group, this figure was reduced to 30%.

Surgical Experiences with Tumors of the Carotid Body, Glomus Jugulare and Retroperitoneal Nonchromaffin Paraganglia. R. T. Sessions, B. McSwain, R. I. Carlson and H. W. Scott Jr. Ann. Surg. 150:808-823 (Nov.) 1959 [Philadelphia].

Neoplasms of the chemoreceptor system have been referred to as chemodectoma, nonchromaffin paraganglioma, or carotid-body tumor. The authors reviewed all tumors of the carotid body and of related structures observed at Vanderbilt University Hospital, Thayer VA Hospital, and 4 other Nashville (Tenn.) institutions. Sixteen carotid-body tumors, 4 tumors of the glomus jugulare, and 2 infradiaphragmatic nonchromaffin paragangliomas were collected over a 30-year period. Of the 16 patients with carotid-body tumors, 10 were treated by simple excision of the tumor. In 3 patients removal of the tumor involved ligation of the common, internal, and external carotid arteries, and in 2 other patients excision of the tumor necessitated ligation of the external carotid artery alone. One patient refused surgery. There was no operative mortality, but only 5 of the 15 patients operated on experienced completely uneventful postoperative courses, while the other 10 showed evidence of neurological damage. The neurological side-effects, which varied from a slight ptosis to hemiplegia and aphasia, were most marked in those patients in whom the internal and common carotid arteries were ligated. The most common mechanism of neurological impairment was operative injury to cranial and cervical sympathetic nerves, such as the vagus, hypoglossal, cervical sympathetic, glossopharyngeal, and spinal accessory nerves. While many of these palsies were transitory, 6 patients have permanent residual neurological impairment.

The anatomic situation of the glomus jugulare in the adventitia of the jugular bulb immediately beneath the floor of the middle ear leads to the development of symptoms only after the tumor erodes into the middle ear or into the cranial vault. The diagnosis of glomus jugulare tumor has been verified histologically in all 4 instances in this series. Two of these patients, both of whom complained of deafness and tinnitus on the involved side, had long histories of chronically draining ears and had previously undergone simple mastoidectomies or "polypectomies" in an effort to control the discharge. A third patient complained only of bleeding from the ear. In each case surgical manipulation of the tumor was associated with copious bleeding, which could be controlled only by packing the middle ear cavity. In the fourth patient the glomus jugulare tumor eroded into the cranial vault and gave rise to signs of brain tumor without either aural symptoms or cranial nerve palsies.

The term "nonchromaffin paraganglioma" is applied to the chemodectomas located in regions other than the head and neck. In the first of the 2 patients with nonchromaffin paraganglioma presented, masses of greatly enlarged lymph nodes were found along the aorta and the pelvic brim during laparotomy. Tissue removed for biopsy revealed clusters of cells in an alveolar arrangement surrounded by a reticulated network containing capillaries and was compatible with nonchromaffin paraganglioma. The second patient with nonchromaffin paraganglioma had a tumor in the retroperitoneal space. The history of this patient illustrates the importance of radical excisional surgery, because of the tendency to invasion and local recurrence of retroperitoneal nonchromaffin paragangliomas. The authors feel that the generally benign biological behavior of tumors of the carotid body and glomus jugulare indicates treatment by simple excision.

Surgical Treatment of Mitral Stenosis with Particular Reference to the Transventricular Approach with a Mechanical Dilator. A. Logan and R. Turner. Lancet 2:874-880 (Nov. 21) 1959 [London].

The authors comment on the difficulties with the atrial approach in the surgical treatment of mitral stenosis. As the result of failures with the atrial approach, they decided to approach the mitral valve from the ventricle and to guide the instrument into position by transatrial palpation. In 1954 one of the authors observed Dubost perform mitral valvulotomy with use of the transatrial dilator, which he had introduced because of dissatisfaction with the finger-and-knife technique. It was intended to follow his technique, and with this in view an expanding dilator was devised. This instrument was first used in a case in which digital valvulotomy had failed. The handle was found to be so shaped that the expanding head could not be directed into the mitral valve. Consequently the instrument had to be introduced through the anterior ventricular wall. The commissures were successfully divided. At first there was much doubt about the propriety of using the ventricular route when the transatrial alternative was so successful in Dubost's hands. This doubt was increased when, in the 6th case in which the transventricular route was used, death from hemorrhage followed shortly after the operation, and the source was believed to be the ventricular wound. During the next year the ventricular route was used only sporadically. When Dubost's instrument became available it was used by the transatrial route in 19 cases, but trouble from entanglement of the instrument in the chordae tendineae and the personal preference acquired for the transventricular route combined to establish the latter as the preferable approach.

The transventricular approach to the mitral valve with a mechanical dilator was adopted in 438 patients requiring valvulotomy. The use of the dilator was associated with a striking increase in the incidence of complete anterior and posterior commissural division and a decrease in incomplete division of both commissures. The operative mortality has been slightly higher (6.4% compared with 5.0%), but the conditions of more patients have been improved. Results have been good in a surprisingly high proportion of cases with heavy calcification of the valves. Death from traumatic mitral incompetence has not been more frequent than with other techniques, but with improved commissural division there has been a slightly higher incidence of postoperative systolic murmurs. What will be achieved at operation cannot be predicted from preoperative examination. In the experience of the authors, the advantages of the use of the transventricular dilator have made it a valuable addition to the techniques of mitral valvulotomy.

Transventricular Mitral Valvotomy: Report of 50 Consecutive Cases. H. B. Crum and M. J. C. Tsapogas. Lancet 2:880-883 (Nov. 21) 1959 [London].

The authors were introduced to the transventricular approach to the mitral valve by Logan in 1956, and their experience with it began in August, 1957. It had been intended to reserve the method for cases where finger-fracture of the commissure was difficult or impossible. The first results were so satisfactory, however, that the method was subsequently employed in every case. This series comprises the first 50 patients operated on by one of the authors. After the operation, patients are nursed in an oxygen tent for the first 12 hours and are allowed up on the third day, early activity being encouraged. All patients receive digitalis before and after the operation. The amount of digitalis is reduced to a suitable maintenance dose in those who are in atrial fibrillation. Patients in regular rhythm are given digitalis only for a few days after the operation.

Three deaths occurred, and the histories of these patients are reported. All 3 were poor-risk patients. Forty-four patients improved greatly, and 2 others have limited improvement; one is not substantially better because of postoperative pulmonary embolism. An impressive feature has been the excellence of the results in those patients in regular rhythm, many of whom are now fully employed in manual work, often with heart-sounds which are normal or very nearly so. Patients with preoperative atrial fibrillation and the 3 patients in whom persistent fibrillation developed after the operation have, all but one, a greatly improved exercise tolerance. There has been no falling off in the activity of those patients operated on 13 to 18 months ago. The "moderate" patients in this group are 2 of the 3 in whom fibrillation became established after the operation.

Study of Two Cases of Operation with Artificial Heart-Lung. G. N. Guastavino, J. A. Wikinski and others. Semana méd. 64:647-655 (Oct. 22) 1959 (In Spanish) [Buenos Aires].

Two patients with heart abnormalities were operated on under extracorporeal circulation, withou hypothermia. These were the first 2 cases of cardiac surgery performed with this technique in Argentina by Argentine surgeons. The apparatus used was a modified oxygenator of the Björk-Kay-Cross type Anesthesia was induced with 2.5% Pentothal and a small dose of succinylcholine. Subsequently endotracheal intubation was instituted. Arterial and venous pressures were manometrically controlled The surgical approach was through a transsterna bilateral thoracotomy, opening of the pericardium widening of the incision to the left, and exploration of the heart.

The first patient was a 14-year-old girl who had received a diagnosis of congenital heart disease and malformations. Atriotomy was performed, and the interatrial defect was found in the upper two-thirds of the septum, measuring 40 by 20 mm. A little lower and behind the septum was a second defect, measuring 10 by 5 mm. The defects and the inferior orifice were sutured. The wound was closed in planes, and bilateral pleural drainage was performed. The postoperative period was uneventful, and the recovery excellent. The second patient, a 5-year-old girl, had an interatrial communication demonstrated by oximetry and catheterization. Atriotomy was performed under extracorporeal circulation, without hypothermia. A large interatrial defect of the ostium secundum type was found, measuring 60 by 40 mm. The defect was sutured with a continuous suture, and the atrial wall was closed. After this procedure, which lasted 18 minutes, a pulmonary arteriotomy was started at 1 cm. above the origin of the valve. As the blood afflux was much larger than was expected, a retrograde digital valvulotomy was performed, and the arteriotomy was closed. When the extracorporeal circulation stopped, the heart sounds were normal. The patient woke and responded to stimuli. Approximately 30 minutes later a hemorrhage occurred, due to hypoplasia of the pulmonary artery. The patient died 7 hours after the operation. The authors believe that atriotomy under extracorporeal circulation, without hypothermia, is the procedure which allows most time and guarantees most precision in the closure of defects of the interatrial septum, especially when there are associated defects.

Corrected Transposition of the Great Vessels. J. Espino-Vela, E. S. de la Parra and G. Anselmi Ch. Arch. Inst. cardiol. Mexico 29:573-598 (Sept.-Oct.) 1959 (In Spanish) [Mexico, D. F.].

The abnormality described as corrected transposition of the great vessels raises a serious diagnostic problem, both in relation to the transposition itself and to the associated malformations which requently occur. Three cases of this transposition re reported. In one patient the diagnosis was esablished by the angiocardiographic findings; in he other 2 it was established by exploration durng surgical treatment for an associated atrial septal efect. The 3 patients had 2 anatomic traits in ommon. (1) the abnormal situation of the great essels (anterior and abdominal aorta and pulnonary artery) and (2) the normal position of the tria. The first patient, a 28-year-old woman, had een cyanotic during the first 8 months of her life. yspnea of effort started at the age of 9 years. alpitation spells of short duration, ending in preordial pain, were the main symptoms in adulthood. he roentgenographic examination revealed thorcic asymmetry, enlarged right ventricle, and small eft ventricle. The angiographic study showed that he pulmonary artery, filled with opaque substance n the first plate, started behind a clear, semilunar pace, which in subsequent plates was identified as he aorta. The diagnosis of corrected transposition f the great vessels was established, and no surgical reatment was attempted because of the possibility hat the defect might have a compensating role (a iew that the authors have abandoned).

The second patient, a 12-year-old girl, had been xamined at different ages and received different iagnoses. Phonocardiographic findings suggested ersistence of ductus arteriosus, while electrocariographic findings suggested an interatrial comnunication of the ostium primum type. At operation he aorta was found before and to the left of the ulmonary artery, which was posterior and situated to the right. The ventricle, situated to the eft, seemed to have an infundibulum. The diagosis of corrected transposition of the great vessels vas established, and the thorax was closed without losing the interatrial communication.

The third patient, a 5-year-old boy, had had narked cardiac murmurs since the age of 3 months. ulging of the precordial area, bronchitis, and crises of temporary cyanosis were his main symptoms. Auscultation and catheterization findings led to the diagnosis of interventricular communication. The patient underwent surgical treatment, during which the great vessels were found transposed. A ventriculotomy was performed, with closure of the interventricular communication. The patient died a few hours after the operation. The authors conclude that in corrected transposition of the great vessels the anatomically right ventricle, which is actually at the left, is able to function as an anatomically left ventricle. The electrocardiographic leads behave as if the ventricles were in their normal position. Because of this misleading electrocardiographic picture, the authors believe that angiocardiography is the best method for diagnosing corrected transposition of the great vessels.

Late Findings After Operations on the Adrenals. H. Eufinger and J. Alslev. Beitr. klin. Chir. 199: 129-142 (no. 2) 1959 (In German) [Munich, Germany].

The authors review operations on 31 patients who, in the course of the 14 years from 1943 to 1957, underwent 36 operations on the adrenals at the surgical clinics of the University of Kiel. Nine operations were carried out for adrenal cortical hyperfunction (Cushing's syndrome), 6 for the adrenogenital syndrome, 6 for paroxysmal hypertension, 8 for chronic hypertension, and 2 for metastasizing mammary cancer. Hyperplasia of the cortex was found in 17 patients, mostly in those with the adrenogenital syndrome or with hypertension but also in 3 of those with Cushing's syndrome. Of the other 6 patients with Cushing's syndrome, 3 had cortical adenoma, 2 had cortical carcinoma, and 1 had a cortical tumor, the histological nature of which could not be clarified. Of the patients with paroxysmal hypertension, 1 had pheochromocytoma; 2, medullary hemorrhages; 1, medullary malacia; and 1, a medullary cyst. In 3 patients, namely, in 2 with chronic hypertension and 1 with paroxysmal hypertension, the adrenals were found to be morphologically normal.

In patients with Cushing's syndrome, the existing tumor was usually extirpated, or unilateral adrenalectomy was carried out, while in patients with the adrenogenital syndrome unilateral or bilateral adrenalectomy was the rule. For paroxysmal hypertension ectomies or resections were performed, and in patients with chronic hypertension interventions on the adrenals were combined with sympathectomy. Patients with mammary cancer were subjected to bilateral adrenalectomy.

Eight of the 31 patients died after the operation, 2 of each of the following: Cushing's syndrome, paroxysmal hypertension, chronic hypertension, and metastasizing mammary carcinoma. Follow-up was possible in 21 of the 23 survivors. Lasting clinical improvement was achieved in 5 of 6 patients with Cushing's syndrome, in none of 5 with the adrenogenital syndrome, in 3 of 4 with paroxysmal hypertension, and in 2 of 6 with chronic hypertension. One patient with Cushing's syndrome and one with chronic hypertension succumbed to their primary diseases, namely, adrenocortical carcinoma and malignant nephrosclerosis, 14 months and 1 month, respectively, after the operation. One patient with the adrenogenital syndrome died in a traffic accident. One patient with chronic hypertension required permanent substitutional therapy. The authors conclude that surgical interventions on the adrenals produce satisfactory results in patients with Cushing's syndrome and in those with paroxysmal hypertension, but not in those with the adrenogenital syndrome or with chronic hypertension.

Regional Enteritis and Crohn's Disease. R. Buchberger. Beitr. klin. Chir. 199:220-236 (no. 2) 1959 (In German) [Munich, Germany].

Crohn and associates in 1932 described a chronic, ulcerating, granulomatous terminal ileitis. Later, the changes characteristic of Crohn's disease were found also in other sections of the gastrointestinal tract, and the concept of regional enteritis evolved. The morphologic concept of regional enteritis includes a series of inflammatory intestinal diseases, which have a segmental involvement. Crohn's disease is probably the most chronic and the most readily recurring form. The author reviews observations on 12 patients with Crohn's form of regional enteritis observed at the second surgical clinic of the University of Vienna between 1933 and 1957. In 11 of the patients the diagnosis was histologically verified. Ten of the patients had had symptoms for from 2 to 10 years. Seven of the patients had undergone appendectomy, one of them several years before the appearance of the symptoms of regional enteritis, but the other 6 appendectomies must be regarded as "operations in a quandary"; they were performed during regional enteritis, and the changes typical of enteritis were observed in the course of some of the operations.

Although this was not the case in the patients reviewed here, acute appendicitis may develop in the course of chronic regional enteritis, either because the enteritis spreads to the appendix or because it impairs the communication between the appendix and the cecum. External fistulas in 3 of the patients could be traced to the appendectomy. One of the patients had had an attack of paratyphoid some years before the onset of regional enteritis. Of the 2 children in the group, one had had a pelvic fracture and the other a vertebral fracture from one to several years before the onset of the regional enteritis, and in this connection the author mentions the traumatic genesis of regional enteritis. Colic-like pain in the lower abdomen was a complaint in all but 2 of the 12 patients. Difficulties with defecation, either diarrhea or constipation, were also frequent. Roentgenologic examination will reveal irregular contours, signs of papilomatous areas in the mucosa, internal fistulas, and defective peristalsis. Stenosis, combined with spasms produces in the roentgenogram "string signs" and "skip areas."

Surgical therapy is indicated only after conservative measures, particularly dietetic therapy, have failed. The primary operations carried out in 11 of the patients included typical ileocecal resection in 7, while the remaining 4 were subjected to one of the following: (1) hemicolectomy; (2) resection of the ileocecum and of a part of the small intestine; (3) resection of part of the small intestine only; and (4) ileotransversostomy. Three patients later required operations for recurrences; 2 of these patients died. Follow-up examination on 8 of the 10 survivors showed that 4 were well, but 2 others, while improved, still had chronic intestinal disturbances. While the 2 children felt well and had developed fairly normally, they still had symptoms and roentgenologic signs of enteritis, which, however, could be controlled by medical treatment.

In the last part of his paper, the author discusses observations on 11 patients with acute terminal ileitis and on 22 with postoperative enterocolitis. The regional appearance of these diseases seems to be due to a disturbance in the neurosympathetic regulation.

Malignant Melanoma: Treatment. J. L. Viaggio, D. Neustadt, R. Jufe and S. Kohan. Rev. Asoc. méd. argent. 73:424-427 (Oct.) 1959 (In Spanish) [Buenos Aires].

Eighteen patients, between the ages of 15 and 85 years, with malignant melanoma were observed. On first consultation, 9 patients had an intact tumor; 3 had an ulcerating bleeding tumor; 2 presented metastases; 1 had a cancer on the scar of a nevus, which had been surgically removed 6 years previously; 1 was blind from melanoma of the choroid; 1 had a tumor on a plaque of varicose angiodermatitis; and 1 had diffuse metastases of a primary tumor of unknown localization. Ten patients had not received any treatment; the remaining 8 had had either a partial biopsy of the melanotic lesion, economical resection with the electric knife, coagulation, or application of carbon dioxide snow. Regional metastases were observed at the first consultation in 9 patients. In one patient the metastases appeared during treatment of the local lesion, and in 7 patients the metastases had not appeared up to the present time, after a short period of observation. The treatment consisted of ample resection of the melanotic lesion and removal of the regional lymph nodes, either immediately or a few weeks after the resection of the primary lesion. In some of the patients the regional lymph nodes were normal before and for 2 years after the resection of the primary lesion. These lymph nodes were surgically removed as soon as they became enlarged. Follow-up of the patients included clinical, roentgenographic, and laboratory examinations every 2 or 3 months.

By the end of 5 years, 3 patients had disappeared from observation, but 8 patients are still living (5 without clinical symptoms and 3 with recurrence of melanoma and lymph node and visceral metastases). Six patients died of melanoma within 5 years of treatment. The authors conclude that malignant melanoma is a highly metastasizing lesion. Its malignancy depends on the size and location of the primary lesion and on the age and biological condition of the patient. The larger the primary lesion, the lower its location in the body (on the sole or in the malleolar region), and the younger the patient, the higher the degree of malignancy. Puberty and pregnancy increase the possibility of malignancy.

Temporal Lobe Tumors: Study of 100 Cases. H. N. Usarralda, E. A. Saint-Martin and others. Prensa méd. argent. 46:1376-1381 (May 29) 1959 (In Spanish) [Buenos Aires].

The authors report on 100 cases of tumors of the temporal lobe in a series of 500 intracranial tumors observed at several hospitals in Buenos Aires during a 10-year period. The patients' ages ranged from 12 to 71 years, with an average of 46. The most frequent types of tumor were glioblastoma-astroblastoma in 22 patients, heteromorphous glioblastoma in 21, meningioma in 19, and metastatic tumors in 11. The metastatic forms were secondary o bronchopulmonary carcinoma and represented 15.7% of the tumors in male patients. Malignant gangliomas represented 55% of the tumors in men and 52% of the tumors in women. The symptoms were headache in 70% of the patients, hemiparesia n 66%, and intracranial hypertension in 49%. Less frequent were mental disturbances, hemianopsia, aphasia, and epilepsy. Carotid angiography, which was performed more frequently in the last than in he first 5 years of the study, provided positive diagnosis in 35 patients. Pneumoencephalography and ventriculography were also used as diagnostic aids.

The treatment of the 100 patients was craniotomy, with an attempt at total resection; this was possible in 47 patients, whereas partial, or subotal, resection was performed on 45. There was no record of the surgical technique for the remainng 8 patients. Twenty-eight patients were alive at the time this article was written. The survivals corresponded to approximately 45% of the patients who underwent total resection and to 13% of those who underwent partial resection, whereas the operative mortality was the same for both types of operation. Forty-seven of the 72 patients who died had a malignant glioma; 10 had metastatic temporal tumors; and 1 had a sarcoma. These figures represented 80% of the malignant tumors.

Clinical Experience with Bronchogenic Carcinoma: A Review of 149 Cases. M. A. Polacek and R. K. Brown. Am. Surgeon 25:944-949 (Dec.) 1959 [Baltimore].

The authors report on 149 male patients with microscopically documented bronchogenic carcinoma, who were treated at the Veterans Administration Hospital in Denver between 1951 and 1958. Of these, 148 were followed up to the end of this period or to death. Over 85% of the patients gave a history of having smoked at least 1½ packages of cigarettes per day for 20 or more years. The findings in this series with regard to age distribution, histological patterns, location of the tumor, symptomatology, and survival rates among the patients with and without resection did not differ significantly from those of the series reported by other workers. Surgical exploration was carried out in 57 patients (38%), with definite extirpation done in 30 patients (20% of the total group). Lobectomy, with indicated dissection of mediastinal nodes, was the chosen procedure and comprised 50% of the resections. Of 52 patients who were operated on more than 30 months ago, 15 had definitive surgical resection. Six of these have lived for 30 to 81 months without evidence of recurrence, a survival rate of 11.5%. A policy which is liberal toward exploratory thoracotomy but conservative in regard to technique of resection has, in this series, given the patient the same long-term survival opportunity, with less postoperative morbidity and mortality, as have the more radical procedures now frequently employed.

Postoperative Chylothorax. W. M. Levi Jr. and E. F. Parker. Am. Surgeon 25:960-964 (Dec.) 1959 [Baltimore].

The authors report the occurrence of postoperative chylothorax in a 50-year-old man one month after a partial esophagectomy with intrathoracic esophagogastrostomy for a probably carcinomatous constricting lesion of the esophagus, and in a 5-year-old girl 5 days after obliteration of a patent ductus arteriosus. Five thoracenteses were performed because of a right-sided chylous effusion in the man; 3,500 cc., 1,150 cc., 2,800 cc., 2,200 cc., and 750 cc., respectively, of milky fluid were removed. The chylous fluid contained fat globules on microscopic examination. Its specific gravity was 1,014. The reaction was alkaline. No further thoracenteses were required. Ten thoracente were performed on the girl, and an aver 1,000 cc. of milky fluid was removed every improvement was achieved in 5 of 6 patients with Cushing's syndrome, in none of 5 with the adrenogenital syndrome, in 3 of 4 with paroxysmal hypertension, and in 2 of 6 with chronic hypertension. One patient with Cushing's syndrome and one with chronic hypertension succumbed to their primary diseases, namely, adrenocortical carcinoma and malignant nephrosclerosis, 14 months and 1 month, respectively, after the operation. One patient with the adrenogenital syndrome died in a traffic accident. One patient with chronic hypertension required permanent substitutional therapy. The authors conclude that surgical interventions on the adrenals produce satisfactory results in patients with Cushing's syndrome and in those with paroxysmal hypertension, but not in those with the adrenogenital syndrome or with chronic hypertension.

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The numerous factors that play a role in the survival of a patient with a gastric resection for neoplasm are complex and often coexistent with many not reviewed or unknown. Recurrent or newly formed carcinoma in the gastric stump is no longer viewed as a formidable fatal experience. Some of these patients may be saved by prompt and adequate secondary surgical procedures. Early recognition of cancer in the residual gastric remnant is difficult because of the long symptomless interval and because roentgenologic diagnosis of the residual stomach pouch is often less informative. Gastroscopy studies at intervals may be indicated.

Intestinal Bleeding and Perforation Complicating Treatment with Vasoconstrictors. R. B. Brown, B. H. Rice and J. E. Szakacs. Ann. Surg. **150**:790-798 (Nov.) 1959 [Philadelphia].

The authors observed 2 unusual cases of intestinal bleeding and perforation. One was that of an 8-year-old girl in whom a large pheochromocytoma was found and was removed. The other was that of a 61-year-old man, who was operated on for aneurysm of the abdominal aorta; to counteract a precipitous drop in blood pressure, he was given large doses of Neosynephrine. Both patients died, and the postmortem examinations revealed gastrointestinal hemorrhage and perforation not associated with the common etiological factors of trauma, infection, obstruction, neoplasm, or occlusion of the larger mesenteric vessels. A proliferative and occlusive arteritis of the smaller vessels in the intestinal wall was evident. The authors raise the question as to whether these intestinal complications could be related in any way to the obvious common factor in these 2 cases, that of exposure to abnormal amounts of vasopressor substances, endogenous in one and exogenous in the other. Further investigation of this possibility was directed into 3 main channels: (1) a review of the literature to learn whether others had observed similar complications in patients with pheochromocytoma or in those who had been treated with vasopressor agents; (2) a study of clinical and pathological material in these 2 categories; and (3) an experiment to determine whether intestinal lesions can be produced in dogs by the administration of levarterenol.

While it has not been possible to prove conclusively that the intestinal hemorrhage and perforation observed in the 2 patients was due to the vasoconstrictors, it has been demonstrated that localized hemorrhages and necrotizing arteritis can be produced in the intestinal wall of dogs by the administration of levarterenol. Further experiments are being initiated to control and quantitate these preliminary observations in terms of dosage of drugs, time intervals, degree of hypertension produced, and plasma catechol amine levels. In the light of the evidence accumulated to date the authors consider gastrointestinal bleeding and perforation as potential complications of the clinical use of these drugs in high concentration and in patients with pheochromocytoma.

NEUROLOGY & PSYCHIATRY

The Electroencephalogram in Parkinson's Syndrome. A. C. England, R. S. Schwab and E. Peterson. Electroencephalog. & Clin. Neurophysiol. **11**: 723-731 (Nov.) 1959 [Montreal].

The authors found that there were increasingly more exceptions to the impression that the electroencephalogram (EEG) in patients with paralysis agitans (Parkinson's disease) is within normal limits, as more and more patients were studied at their special clinic, which is now in its 10th year. When they began to refer their patients for neurosurgical interventions, they began to look for laboratory tests that might lead to better selection of patients for surgical treatment. In 1957 they began to collect a new series of electroencephalograms of patients with paralysis agitans.

Thirty-nine of 75 patients with paralysis agitans were found to have an abnormal EEG. The abnormality was usually a random, diffuse, slow activity in the theta and delta range, most often restricted to the posterior portion of the head, occasionally dominant on one side or less commonly restricted to one side. There was no obvious correlation with the clinical diagnoses of postencephalitic, arteriosclerotic, or idiopathic types of paralysis agitans. The authors found this clinical subclassification of very limited usefulness. Abnormalities in the EEG were not related to the age of the patients or to the duration of the disease. They days. Observations on the thoracentesis fluid included: specific gravity, 1,010; serum lipids, 9,113 mg. per 100 cc.; cholesterol, 125 mg. per 100 cc.; total proteins, 1.09 Gm. per 100 cc. On the 28th postoperative day, the patient underwent thoracotomy through the previous incision; 800 cc. of chyle was present in the left pleural cavity. On opening the chest and retracting the lung, chyle was visible, leaking from a defect in the mediastinal pleura, about 3 cm. distal to the aortic end of the divided ductus arteriosus. The mediastinal pleura was reopened in this area. The thoracic duct was dissected. A small defect in the duct was found, from which chyle emerged. The duct was divided at the site of the defect, and its proximal and distal ends were ligated with silk. The chest was closed with drainage, and the child made an uneventful recovery.

Chylothorax is the presence of chyle in the pleural cavity, secondary to a loss in continuity of the thoracic duct, at a level above the aortic hiatus, with a fistula into the pleural cavity. Twenty-two cases of chylothorax occurring in patients after cardiovascular and other intrathoracic operations were collected from the literature. Eight of these 22 patients required reoperation and were treated successfully by ligation of the thoracic duct. Of the authors' 2 patients, one required reoperation and was treated successfully by ligation of the thoracic duct, while the other recovered with conservative treatment.

Antrectomy with Vagectomy for Chronic Duodenal Ulcer. L. T. Palumbo, W. S. Sharpe, D. J. Lulu and others. Surgery 46:1005-1011 (Dec.) 1959 [St. Louis].

The authors report on 115 consecutive male patients, between the ages of 24 and 71 years, who underwent antrectomy with bilateral infradiaphragmatic vagus resection for chronic duodenal ulcer at the Veterans Administration Hospital in Des Moines, Iowa, between 1957 and 1959. There was one postoperative death (0.87%), which was due to an acute necrotizing pancreatitis. No deaths occurred in 23 patients (22%) on whom the operation was performed as an emergency procedure during the time of continued and/or massive bleeding. On 85% of the patients the operation was performed by the senior house officers under the direct supervision of the full-time surgical staff. The operating time required was at least one-half of that of a partial gastrectomy with or without a vagus resection. The hospital stay was shortened by 2½ days, as compared with that required for other surgical procedures formerly used by the authors for chronic duodenal ulcer. Achlorhydria has persisted in 75 patients for 12 to 18 months postoperatively, and it is unlikely that a recurrent or marginal ulcer will develop in this group of patients. All patients gained weight after the operation. Ninety-five per cent of the patients maintained themselves on 3 meals a day with an occasional snack between meals, without any major restrictions in dietary measures. Diarrhea and the dumping syndrome were infrequent and were not seriously handicapping any patient. The over-all evaluation of the results in the 115 patients was considered excellent to good in 94% of them.

Antrectomy with bilateral infradiaphragmatic vagus resection is at present the authors' operation of choice for chronic duodenal ulcer. Its advantages include lower morbidity and mortality, more rapid rehabilitation, less side-effects, shorter operating time and hospital stay, least chance, if any, for recurrent or marginal ulcer formation, and over-all results superior to practically all other operative procedures.

Factors in Long-Term Survival of Carcinoma of the Stomach: Two Case Reports of 21- and 23-Year Survival. L. Sperling and L. Kaplan. Am. Surgeon 25:976-985 (Dec.) 1959 [Baltimore].

The authors report on a 54-year-old woman and a 75-year-old man, both of whom had undergone subtotal gastric resection for carcinoma of the stomach 21 and 23 years previously. On reexamination, the woman was well and free of symptoms; there was no evidence of recurrent carcinoma. The man, however, complained of a 30-lb. (13.6-kg.) loss of weight in 3 months, anorexia, postprandial distress, and progressive weakness. There was a suggestive mass in the left upper quadrant of the abdomen. Surgical exploration revealed an indurated mass at the site of the previous retrocolic gastrojejunostomy. The stomal mass, one-half of the remaining stomach, and both the efferent and afferent loops of the jejunum were resected along with the adjacent jejunal mesentery. The old duodenal stump was exposed, and a Billroth 1 gastroduodenostomy was made. The gastric malignancy observed in the operative specimen, despite slight morphologic differences, was sufficiently similar to that observed 23 years ago to suggest relatedness, and the localization to the gastrojejunostomy stoma and adjacent tissue strangely suggested a much delayed recurrence. One year after the second operation the patient was still feeling good, despite the palliative nature of the resection.

The survival of the woman appeared to be the function of the presence of a stage 1, fungating, polypoid, exophytic, antral adenocarcinoma, which was within the lines of transection surgically, had not extended to serosa or neighboring tissues, and had not metastasized to the lymph nodes. In the man, the initial operative specimen revealed a stage 3, large crater-forming, ulcerating, elevated, antral adenocarcinoma, which had extended to serosa, omentum, and mesentery, and had metastasized to regional lymph nodes by the time of the

Among the 600 children of group 2, the prematurely born children were found to come from a poorer socioeconomic background than the mature controls. When the premature infants were matched for sex, family placing, and social background with children mature at birth, it was found that there was no difference in subsequent mental development between those premature infants who weighed more than 4½ lb. at birth and the control group. Among the children with a birth weight of 4½ lb. or less, there was an increasing proportion of dull, retarded, and grossly defective children as birth weight decreased. When the mothers of handicapped children were compared with those of infants of like birth weight but without handicap, and with those of mature controls, the following factors appeared to be of importance in the handicapped group: 1. There was an excessive number of older mothers. 2. The incidence of poverty was strikingly high. 3. There were higher incidences of previous and subsequent abnormal pregnancies and of relative infertility.

The Outcome of Pregnancy in Diabetic Women: I. Fetal Wastage, Mortality, and Morbidity in the Offspring of Diabetic and Normal Control Mothers. A. Dekaban and R. Baird. J. Pediat. 55:563-576 (Nov.) 1959 [St. Louis].

The 48 diabetic women investigated were selected from a number of hospitals on the basis of 2 criteria: 1. The women were under 43 years of age. 2. They had had at least 2 pregnancies after the diagnosis of diabetes had been established. The authors interviewed all the mothers and personally examined most of their offspring. When no personal contact with the children was possible, a medical report from the family or school physician was obtained. A control mother for each diabetic mother was chosen from the same hospital in which the diabetic subject had had her last delivery. All terminations of pregnancy before 26 weeks were classified as abortion. All deaths within 4 weeks from birth were classified as neonatal death. The surviving offspring was regarded as abnormal if there was a severe congenital malformation or an intellectual or neurological deficiency interfering seriously with the spontaneous activities appropriate to the child's age. Of the 48 diabetic mothers, 9 had a mild degree of the disease, i. e., they required only a diet, or a diet plus a daily insulin dose not higher than 20 units; 22 had moderate diabetes (requirement of a diet plus a daily insulin dose of 20 to 40 units); and 17 had severe diabetes (diet plus an insulin requirement of more than 40 units daily).

There were 157 pregnancies among the 48 diabetic mothers. Their outcome was abortion in 47 (29.9%), stillbirth in 18 (11.5%), neonatal death in 13 (8.3%), surviving abnormal child in 6 (3.8%), and surviving normal offspring in 73 (46.5%). There were 78 pregnancies among the same women during their prediabetic stage, with the following outcome: 16 abortions (20.5%), 4 stillbirths (5.1%), 1 neonatal death (1.3%), 2 abnormal (2.6%) and 55 (70.5%) normal surviving children. Among the 48 normal controls there were 249 pregnancies with the following outcome: 31 abortions (12.4%), 3 stillbirths (1.2%), 9 neonatal deaths (3.6%), 1 surviving abnormal child (0.4%), and 205 surviving normal children (82.3%). The total pregnancy wastage in the sample of diabetic mothers was 49.5%—3 times higher than the wastage rate (17.2%) in the sample of normal matched controls. The total wastage of pregnancy during the prediabetic stage was 26.9%, which is higher than in the normal controls but much lower than in the diabetic stage. There was no significant difference associated with the degree of diabetes, or with the occurrence of complications during the pregnancy.

Significant differences were found in association with adequate control of the diabetes at the time of delivery, and with the type of delivery. In the group of 39 deliveries carried out by cesarean section or after induction, the total incidence of stillbirths, neonatal deaths, and live abnormal offspring was 20.6%, whereas in the group of spontaneous deliveries this incidence was of 40.8%. This difference suggests that the outcome of pregnancy was more satisfactory when the delivery took place 2 or 4 weeks before term, by means of cesarean section or after induction. There were 6 surviving abnormal children in the sample of 157 pregnancies of diabetic women, while in the control sample of 249 pregnancies there was one only. The difference in percentages (7.6 and 0.4%, respectively) is significant at $p < 0.01$. The abnormalities in these children included mental deficiency, congenital malformations, birth injury, and epilepsy.

The Outcome of Pregnancy in Diabetic Women: II. Analysis of Clinical Abnormalities and Pathologic Lesions in Offspring of Diabetic Mothers. A. S. Dekaban. J. Pediat. 55:767-776 (Dec.) 1959 [St. Louis].

The author analyzes the factors involved in the stillbirths, neonatal deaths, and live abnormal offspring of 48 diabetic mothers who were investigated in part 1 of this study. Autopsy was performed on the 18 stillborn infants in this sample and on 11 of the 13 infants who died during the neonatal period. Follow-up studies were made of the 6 live abnormal children. The findings were grouped into 5 main categories: (1) stillbirths without evident major lesions, although some infants were edematous; (2) pulmonary hyaline membrane disease; (3) congenital malformations; (4) birth injuries; and (5) mental deficiency.

were most closely related to the existence of those phenomena of paralysis agitans entitled "akinetic," and their appearance was an unfavorable sign for basal ganglion neurolytic surgery, as well as for improvement by the commonly used medications.

The preliminary observations from depth recording, in connection with surgery in paralysis agitans on the globus pallidus and related structures, appeared unfruitful, as they disclosed nothing that could be distinguished as a source of either tremor or rigidity. The postoperative records, in contrast, demonstrated that a permanent focal slow-wave focus is usually produced by destructive operations on the basal ganglions.

Electrocardiographic Changes in Poliomyelitis Patients. R. T. McReynolds and O. L. Huddleston. Arch. Phys. Med. 40:489-491 (Nov.) 1959 [Chicago].

Electrocardiographic studies were made on 70 patients with poliomyelitis, who were severely paralyzed with either the spinal or the bulbospinal type. Four of the patients had severe respiratory paralysis and required the use of the respirator for a period of 5 to 15 months. Six patients showed electrocardiographic changes indicating myocardial involvement, and these changes persisted for a period of 7 to 12 months after the onset of poliomyelitis. None of the patients gave any history of rheumatic fever or heart disease prior to the onset of poliomyelitis. Only 4 of the 70 patients were children; the ages of the adults ranged from 25 to 45 years. The most common abnormalities noted were found in the T waves (low isoelectric or inverted in leads 2 to 6), depression of or abnormal S-T segments, and abnormalities of the QRS complex. The abnormalities are regarded as possibly permanent in nature. This interpretation, however, is to be checked in most of these patients after an interval of more than 5 years.

Some Evidence of a Relationship Between Hodgkin's Disease and Intelligence. L. LeShan, S. Marvin and O. Lyerly. A. M. A. Arch. Gen. Psychiat. 1:477-479 (Nov.) 1959 [Chicago].

It has been a recurring impression that patients with a diagnosis of Hodgkin's disease seem to be of more than average intelligence. However, no objective data on a representative group of patients have been reported in the literature. With this in mind, 408 partial or complete clinical records of Army personnel who had received the diagnosis of Hodgkin's disease during the period 1942-1945 were studied for evidence of the general intelligence level of this group. The mean Army General Classification Test (AGCT) score for 97 white enlisted men, whose cases were diagnosed as Hodgkin's disease during World War II, was found to be significantly higher than that for the Army population mean. In 209 cases of Hodgkin's disease among white male enlisted men, the greater proportion of prewar occupations was found to be in those occupational groups whose median AGCT scores were highest. The data yielded no significant relationship between AGCT scores and severity of the disease, as indicated by duration or histological type. The authors offer no interpretations or attempts to account for these findings.

Urinary Excretion of Phenolic Acids by Normal and Schizophrenic Male Patients. J. D. Mann and E. H. LaBrosse. A. M. A. Arch. Gen. Psychiat. 1:547-551 (Nov.) 1959 [Chicago].

The urinary excretion of phenolic acids by male schizophrenic patients and normal male subjects while on a supposedly uniform diet was investigated. A statistically significant difference between the 2 groups was found for 4 phenolic acids. Since these same compounds had been reported as metabolic products of substances present in coffee, a careful examination of the coffee-drinking habits of the subjects under study was made. The excretion of these 4 compounds and 2 others, in addition, was found to correlate at a highly significant level with coffee drinking. The authors feel that this finding emphasizes the importance of a careful search for uncontrolled variables when metabolic differences are found between schizophrenic patients and normal controls, and the high sensitivity of paper chromatographic methods to certain dietary variables.

PEDIATRICS

Physical and Mental Handicap in the Prematurely Born. C. M. Drillien. J. Obst. & Gynaec. Brit. Emp. 66:721-728 (Oct.) 1959 [London].

The data presented were obtained from 2 groups of children: Group 1 consisted of 92 children, born between 1948 and 1959, whose weight at birth was 3 lb. (1,361 Gm.) or less, and group 2 consisted of 600 children, born between 1953 and 1955, approximately two-thirds weighing 5½ lb. (2,495 Gm.) or less at birth, and one-third being mature controls. Of the prematurely born, about one-half weighed 4½ lb. 2,041 Gm.) or less at birth. These children have been seen at regular intervals since birth. A study of the later development of the 92 prematurely born children in group 1 revealed that the majority were considerably retarded in weight and to a less extent in height; only 11% were at, or above, the expected weight for their age. Fourteen per cent had an estimated IQ of less than 70 and will need special schooling; 49% with an IQ of between 70 and 85 were considered very dull; only 13% were considered average or above average in intelligence. Twenty-two per cent of the children in group 1 have a major physical handicap.

Oestrogen and Psychosexual Disorders. L. H. Whitaker. M. J. Australia. 2:547-549 (Oct. 17) 1959 [Sydney].

It has been routine surgical practice to administer preoperatively large doses of estrogen to adult males who are to be circumcized. This is done with a view to inhibiting the erectile mechanism for some time after operation, so that healing will not be impaired by the occurrence of spontaneous erections. When estrogen has been administered to prevent orchitis after infective parotitis, men so treated reported impotence for some weeks after such treatment. These observations suggested that estrogen might inhibit male sexuality at psychological and physiological levels, and that, if this were true, it might be useful in the treatment of the paraphilias, the more so since reports indicate that castration and irradiation of the testes are not dependable methods of treatment.

The author presents observations on 26 patients who were treated with estrogen. This group included 9 patients with facultative homosexuality, 7 true constitutional homosexuals, 5 with abnormally powerful heterosexual drive, 2 exhibitionists, and 3 with miscellaneous disorders. In 18 cases in which it was desired to inhibit completely sexual desire and the erectile mechanism, it was decided to administer daily 5 mg. of Stilbestrol by mouth for 2 weeks. The shortest period of complete inhibition was 6 weeks, while the longest was 6 months. In 8 cases in which it was desired merely to reduce the intensity of libidinal drive to a controllable level, 1 mg. of Stilbestrol was given daily until the patient first noticed a reduction in his drive. With one exception, oral administration of estrogen to 26 patients presenting with a variety of psychosexual disorders produced the anticipated effects. This form of treatment controls, but does not cure, the deviation of aim or object of the sexual drive. Treatment must be repeated at intervals if it is to be effective.

THERAPEUTICS

The Antineoplastic Effect of a Cyclic Phosphamide Ester of Nitrogen Mustard (Endoxan, or B 518): Clinical Experience. S. Di Pietro. Minerva med. 50:3450-3454 (Oct. 27) 1959 (In Italian) [Turin, Italy].

The author reports the effect of a new antineoplastic drug, cyclophosphamide (Endoxan [B 518]), on 36 patients, 11 with malignant lymphogranuloma, 5 with lymphosarcoma, 7 with reticulosarcoma, 7 with nondifferentiated carcinoma, 4 with sarcoma, and 2 with melanoblastoma. The total dose given intravenously amounted to 4 Gm. The maintenance dose amounted to 50 to 100 mg. per day by mouth or, when given intravenously, to 200 mg. once or twice per week. The drug was well tolerated by most patients, but one patient vomited, and 3 women suffered a temporary loss of hair. The average leukocyte count in 30 patients was 4,000 per cubic millimeter; the leukocyte count remained above 5,000 in 14 patients, was below 5,000 in 14, and was 3,000 in 2. The lowest leukocyte count was observed after 7 days of treatment in 1 patient, after 15 days in 3 patients, after 20 days in 6, after 15 and 20 days in 2, after 15 and 25 days in 2, and after 80 days in 1. The erythrocyte count of 30 patients remained stationary after the treatment in 6 patients, but it increased in 4 and declined in the remaining 20.

The best effect of Endoxan was obtained in those forms of neoplasm most sensitive to antimitotic drugs and especially to nitrogen mustard. Satisfactory results were obtained in the patients with malignant lymphogranuloma; good results were obtained in 2 patients with lymphosarcoma; and very good results were obtained in the patients with reticulosarcoma. In carcinoma, sarcoma, and melanoblastoma, Endoxan had an effect in more than one patient superior to the effect obtained with other drugs. The results in these patients, however, were partial and did not last long. Remission of from 5 to 9 months was observed in patients with lymphogranuloma, lymphosarcoma, and reticulosarcoma. Remission lasted longer in the patients who received a maintenance dose.

The author believes that, because of its low toxicity and the good tolerance shown by most patients, Endoxan may be employed in combination with roentgen-ray treatment. Roentgen-ray treatment, begun shortly after treatment with Endoxan in 5 patients with lymphogranuloma, in 3 with lymphosarcoma, in 1 with reticulosarcoma, and in 1 with round-cell sarcoma, was very effective in inducing a complete regression of the neoplastic masses which had already been partially reduced by Endoxan. The effect of combined treatment with Endoxan and roentgen rays on the hemopoiesis was similar to that observed in patients treated with roentgen-ray therapy alone.

Clinical Observations on a New Oral Diuretic: Chlorothiazide. E. Dispensa and M. Cagnacci. Policlinico (sez. med.) 66:402-421 (Oct.) 1959 (In Italian) [Rome].

The authors report on the effect of chlorothiazide, a new diuretic, on 67 patients, 46 with chronic cardiac insufficiency, 9 with cirrhosis of the liver, and 12 with chronic nephritis; all of them had pronounced edema and marked oliguria. Chlorothiazide was administered orally in a dose of 2 Gm. per day, divided into 4 daily subdoses of 500 mg.

The cause of the increased rate of stillbirths in diabetic mothers is still unknown. Serious disturbances in tissue respiration and electrolyte and hormonal imbalance are the most accepted factors. Pulmonary hyaline membrane disease was diagnosed in 8 of the 11 infants who died during the neonatal period. Six malformations were found in this series, namely, 2 skeletal anomalies in the form of aplasia and dysgenesis; 2 congenital heart abnormalities; 1 microphthalmia with hypoplasia of the retina and of the optic nerve; and 1 communicating hydrocephalus which became apparent at 6 weeks of age. With the exception of the latter, embryonal development must have been disturbed before the 10th week of pregnancy. Although the immediate cause of these congenital malformations is still undemonstrated, hypoglycemia, ketosis, and hormonal disturbances can be suspected. Birth injuries of a mechanical type were present in 3 offspring. The first was a stillborn infant with massive cerebral hemorrhage; the second died within 15 minutes after the birth; and the third had brachial plexus palsy and epilepsy. The oversize of children of diabetic mothers who are delivered spontaneously at term is probably a factor in the occurrence of these injuries. Mental deficiency was the only major abnormality in 2 of the 6 surviving abnormal children studied. No specific underlying lesion could be demonstrated in them.

Disseminated Herpes Simplex in the Newborn. T. Bird and P. S. Gardner. Brit. M. J. 2:993-996 (Nov. 14) 1959 [London].

Herpes simplex virus may produce in children with eczema a severe generalized infection called Kaposi's varicelliform eruption or eczema herpeticum. At first this was thought to be only an involvement of the skin, but widespread concomitant visceral lesions have since been described. Another severe form of disseminated visceral herpes occurs in the absence of eczema; this was first reported from the United States in 1951-1952, and thereafter in England and Australia. The postmortem and histological appearances are fairly characteristic, but establishment of the diagnosis depends on the isolation of the virus. This has been accomplished in only a few cases.

The patient presented was a male infant who had been born at term. He never cried or moved much and ate poorly. The abdomen was noticed to be rather full during the third week, and on the day of admission to hospital, at 21 days, he became suddenly pale and collapsed, with rolling eyes and continuous moaning, but no convulsions. He was pale and thin, with involuntary writhing movements of the limbs. There were a large left parieto-occipital cephalhematoma and a small blister on the back. The abdomen was distended; the liver and spleen were enlarged. No abnormality was found in the chest, but breathing appeared to be embarrassed by the large liver. The infant died 3 hours after admission. The clinical diagnosis was cirrhosis, probably due to reticuloendotheliosis or a storage disease. Characteristic focal lesions were found in the liver and adrenals, but intranuclear inclusions were scanty. The diagnosis of disseminated herpes simplex was definitely established by the isolation of the virus from the liver in tissue culture.

ENDOCRINOLOGY

Cushing's Syndrome Due to Adrenocortical Carcinoma in a 34-Month-Old Girl: Clinical, Laboratory, and Anatomicopathological Study of a Case: Review of Literature. J. M. Cerviño, A. Navarro J. A. Folle and others. An. Fac. med. Montevideo 44:36-52 (Jan.-April) 1959 (In Spanish) [Montevideo Uruguay].

Although adrenal cortical hyperfunction (Cushing's syndrome) is rare in children, it occurs more frequently among girls than among boys. In the cases previously reported the syndrome was caused by an adrenocortical carcinoma. Of the 18 cases reported in the literature, 13 were those of children between the ages of 2 and 13 years and were those of infants between the ages of 3 and 10 months. The tumor probably developed during the fetal life. The subject of this report was a twin girl, born at the 8th delivery to a normal multipara. The patient was observed for the first time at the age of 23 months with the Cushing syndrome completely developed. Her parents, brothers, and sisters, including the twin sister, were normal, but an older sister had died at the age of 15 months with this syndrome. The maternal grandmother had goiter and hyperthyroidism.

Diagnosis of a malignant adrenocortical tumor was made on the basis of the typical symptoms the age of the patient, the high values of ketosteroids and gonadotropins in the urine, and the positive Allen, Hayward, and Pinto tests. The metabolic changes consisted of hyperlipemia, hypercholesterolemia, hyperglobulinemia, and hypocalcemia, as well as increased alkaline reserve and pathological curves of glycemia and polyuria. Death occurred at the age of 34 months from cardiac insufficiency and hypertension. Autopsy showed right adreno cortical carcinoma, necrosis and suppuration of the left adrenocortical tissue, and metastases into the left lung and the liver. There was hyalinization of the basophilic cells of the hypophysis, angiosclerosis and calcification of the renal tubules, serofibrinous pleurisy, hypertrophy of the heart, passive pulmonary congestion, diffuse osteoporosis, and diffuse adipose tissue.

to reproduce the miliary pattern exactly by roentgenography of a whole-lung section after inflation and fixation. The authors feel that mitral pulmonary hemosiderosis, seen roentgenologically, is no contraindication to mitral valvotomy. Successful valvotomy may be followed by gradual disappearance of the miliary infiltration.

Cancer Cells in the Circulating Blood. R. A. Malmgren and J. F. Potter. South. M. J. 52:1359-1362 (Nov.) 1959 [Birmingham, Ala.].

Cytological evaluation of cancer cells was made in 183 blood specimens obtained from 121 patients with various types of cancer, 20 ml. of blood being collected from the antecubital vein in all the patients, and, in addition, 10 ml. of blood being drawn from the vein draining the tumor site in the patients who were operated on. When the cancer types in which there were enough cases to warrant analysis were studied, i. e., 13 patients with carcinoma of the breast, 17 with melanoma, 16 with choriocarcinoma, and 12 with connective tissue sarcoma, cancer cells were demonstrated in the blood of 20 to 39% of these 58 patients, as compared with cancer cells found in an average of 28% of the total series. It is of interest that there were relatively few positive cytological findings in the blood of patients with cancer of the kidney, thyroid, lung, and of unknown localization. The percentage of tumor cells was higher in the blood draining the tumor site (55%) than in the blood from the antecubital vein (24%). Single cancer cells were also more numerous in the blood draining the tumor site than in the peripheral blood. These cells were more often present in the peripheral blood of a patient in whom cancer cells had previously been found than in that of one in whom no cancer cells had been previously demonstrated. No tumor cells were found in the blood of several patients with metastases, but a large number of cancer cells were found in the blood of some patients without any clinical evidence of metastasis. In some blood specimens the cancer cells were in groups and appeared cytologically undifferentiated. The relationship of the circulating cancer cells in the blood to the ultimate course of the disease in a given patient is not known.

Liver Cell Necrosis in Chlorpromazine Jaundice (Allergic Cholangitis): A Serial Study of Twenty-Six Needle Biopsy Specimens in Nine Patients. S. Zelman. Am. J. Med. 27:708-728 (Nov.) 1959 [New York].

The course of jaundice induced by the administration of chlorpromazine was observed during periods which varied from 43 days to more than 3 years in 9 patients of a psychiatric hospital. There were 7 men and 2 women whose ages ranged from 28 to 69 years. Peripheral blood eosinophilia was observed in 7 patients. The serum total bilirubin was elevated in all 9, the peak values varying from 1.9 to 25.3 mg. per 100 cc. The serum alkaline phosphatase reached its peak value at the time of the peak serum bilirubin, or within 11 days thereafter. Rises in the total lipids were observed in the 4 patients for whom this determination was available. The serum glutamic pyruvic transaminase was determined in 6 patients and was elevated in all of them. The serum glutamic oxalacetic transaminase was elevated in 4 of these and remained normal in 2. Liver enlargement was detected by palpation or by roentgenologic examination.

A total of 26 needle aspiration biopsies were performed, varying from 1 to 5 specimens per patient. Cholestasis was apparent in the earliest specimens as granules of bile pigment within cytoplasms of the centrolobular liver cells; later specimens showed distended canaliculi containing large, deeply stained masses of pigment. Some degree of portal fibrosis was found as early as the 25th day of illness and as late as 16 months after the onset. Unicellular liver-cell necrosis was found in significant extent in all 9 patients. Regeneration of liver cells was evident in the centrolobular zones of all the patients, while necrosis of interlobular bile ducts occurred in 2. The findings suggest that necrosis of liver cells (hepatitis) may play a more important role in the causation of chlorpromazine jaundice than is generally recognized. The disease is of prolonged duration histologically, although it has a transitory symptomatology. This duration is reflected in the laboratory measurements, particularly in the serum alkaline phosphatase and often in persisting eosinophilia. There was no evidence of the development of permanent residual damage or fibrosis in the liver in any of the 9 patients reported, although a transient portal fibrosis was observed after resolution of the portal infiltration. The necrosis and subsequent regeneration observed in 2 patients suggest the extension of a destructive process ordinarily limited to the intralobular cholangioles.

PHYSIOLOGY

A Study on the Possible Bronchodilating Effect of Corticotropin (ACTH) in the Therapy of Bronchial Asthma. E. Cerchiai. Minerva med. 50:3078-3084 (Sept. 29) 1959 (In Italian) [Turin, Italy].

The author reports an experimental study on the possible direct effect of corticotropin (ACTH) on the bronchial muscles of the isolated lungs of guinea pigs. The results of this study seem to warrant the hypothesis that the antiasthmatic effect of corticotropin may occur through a direct, pharmacodynamic effect of corticotropin itself, with the need of no other mediating factors, this every 6 hours, in 8-to-15-day cycles repeated at intervals of 5 to 6 days. The drug was administered in 4-to-5-day cycles in some patients, and in cycles of up to 20 days each in others. Diuresis was observed after 48 hours of treatment in 42 of the 46 patients with cardiac insufficiency. A direct relationship between the increased output of urine and absorption of the edema was noticed. The drug had no effect on the remaining 4 patients, who presented heart decompensation complicated by infection and who died. An increase in the elimination of chlorine, of sodium especially in patients with anasarca, and of potassium was observed. Chloremia, sodemia, and potassemia declined a few days after the beginning of treatment. Chlorothiazide had no effect on the function of the kidney or on the blood bicarbonate of the patients with heart disease.

One of the 12 patients with nephrosis presented increased albuminuria; the others presented moderate albuminuria and a marked water salt retention. Two patients suffered from hyposthenuria, and 2 from isosthenuria. Chlorothiazide was always followed by diuresis and increase in the quantity of sodium, potassium, and chlorine excreted. The effect of the drug, however, in these patients was not as marked and as constant as the effect obtained in patients with heart disease. The best results were obtained in patients with chronic nephritis who also presented cardiac complications. Arterial pressure fell in these patients.

The administration of chlorothiazide was followed by an increase in the excretion of water and cations and a slower formation of ascites in the patients with cirrhosis of the liver. A marked potassium excretion was a characteristic effect of the drug in this last group of patients, some of whom received the drug for periods of up to 20 consecutive days. A decline in sodemia and potassemia was observed only 7 to 10 days after the beginning of treatment. The drug was well tolerated by all the patients, and no relevant side-effect derived from its administration. Stranguria, which was observed after some days of treatment in a few patients, disappeared as soon as the drug was withdrawn. Chlorothiazide causes a fall in arterial pressure, but it also potentiates markedly the effect of ganglionoplegic drugs, and especially of mecamylamine which cannot be given in large quantities because it may cause serious side-effects. The mechanism by which chlorothiazide potentiates the effect of mecamylamine appears to be related to the reduced excretion of mecamylamine, which thus remains longer in the organism and has a better hypotensive effect even though the dosage is not increased. This phenomenon, however, seems to be present only during the first days of combined therapy with the 2 drugs.

PATHOLOGY

Serum Vitamin B_{12} Levels in Liver Disease. D. C. Cowling and I. R. Mackay. M. J. Australia 2:555-562 (Oct. 17) 1959 [Sydney].

Raised serum levels of vitamin B_{12} have been observed in liver disease, particularly in the presence of parenchymal cell damage and necrosis. The authors assayed the vitamin B_{12} level in the serum of 57 patients with various types of liver disease, in order to correlate the serum vitamin B_{12} levels with the clinical status, biochemical findings, and histological changes. Raised serum levels of vitamin B_{12} were demonstrated in neoplastic and diffuse parenchymatous liver disease. Levels were highest in acute necrosis and in metastatic cancer of the liver. The raised levels in active chronic hepatitis and nutritional hepatitis usually, but not always, paralleled the activity of the disease as assessed by biochemical and biopsy criteria. Both release of stored vitamin B_{12} from necrosed liver cells and an increase in the vitamin B_{12} binding capacity of the serum may account for elevated serum vitamin B_{12} levels. Biliary obstruction and increased vitamin B_{12} absorption from the intestine were considered unimportant factors.

Association of Cardiac Pulmonary Haemosiderosis and Fibrosis. P. Ellman and R. A. M. Oliver. Brit. M. J. 2:988-990 (Nov. 14) 1959 [London].

Pulmonary hemosiderosis in association with valvular heart disease was reported by Fahr in 1928, when he described autopsy studies on 2 patients with mitral stenosis and on 1 with aortic incompetence. This endogenous hemosiderin has been supposed to lead to pulmonary fibrosis, and the term "brown induration" has been used to summarize the changes. Recent experience with 2 patients under the care of one of the authors has led them to believe that endogenous hemosiderin in the lungs may be less fibrogenic than has been supposed hitherto.

The 2 patients had mitral stenosis, but no significant pulmonary fibrosis developed. In one of these patients, chest roentgenograms had shown a miliary pattern for 18 years, and, since the lung fields cleared gradually after successful mitral valvotomy, it was concluded that the opacities were due to hemosiderin unassociated with fibrosis. The other patient had a 6-year history of hemoptyses, and a miliary roentgenologic pattern had been noticed in the chest when he was first seen in 1954. A satisfactory valvotomy could not be performed, owing to calcification of the mitral valve. The patient died of pulmonary edema after a cerebral embolism. The lungs showed heavy focal hemosiderosis but no significant fibrosis, either macroscopically or microscopically. It was possible to reproduce the miliary pattern exactly by roentgenography of a whole-lung section after inflation and fixation. The authors feel that mitral pulmonary hemosiderosis, seen roentgenologically, is no contraindication to mitral valvotomy. Successful valvotomy may be followed by gradual disappearance of the miliary infiltration.

Cancer Cells in the Circulating Blood. R. A. Malmgren and J. F. Potter. South. M. J. 52:1359-1362 (Nov.) 1959 [Birmingham, Ala.].

Cytological evaluation of cancer cells was made in 183 blood specimens obtained from 121 patients with various types of cancer, 20 ml. of blood being collected from the antecubital vein in all the patients, and, in addition, 10 ml. of blood being drawn from the vein draining the tumor site in the patients who were operated on. When the cancer types in which there were enough cases to warrant analysis were studied, i. e., 13 patients with carcinoma of the breast, 17 with melanoma, 16 with choriocarcinoma, and 12 with connective tissue sarcoma, cancer cells were demonstrated in the blood of 20 to 39% of these 58 patients, as compared with cancer cells found in an average of 28% of the total series. It is of interest that there were relatively few positive cytological findings in the blood of patients with cancer of the kidney, thyroid, lung, and of unknown localization. The percentage of tumor cells was higher in the blood draining the tumor site (55%) than in the blood from the antecubital vein (24%). Single cancer cells were also more numerous in the blood draining the tumor site than in the peripheral blood. These cells were more often present in the peripheral blood of a patient in whom cancer cells had previously been found than in that of one in whom no cancer cells had been previously demonstrated. No tumor cells were found in the blood of several patients with metastases, but a large number of cancer cells were found in the blood of some patients without any clinical evidence of metastasis. In some blood specimens the cancer cells were in groups and appeared cytologically undifferentiated. The relationship of the circulating cancer cells in the blood to the ultimate course of the disease in a given patient is not known.

Liver Cell Necrosis in Chlorpromazine Jaundice (Allergic Cholangitis): A Serial Study of Twenty-Six Needle Biopsy Specimens in Nine Patients. S. Zelman. Am. J. Med. 27:708-728 (Nov.) 1959 [New York].

The course of jaundice induced by the administration of chlorpromazine was observed during periods which varied from 43 days to more than 3 years in 9 patients of a psychiatric hospital. There were 7 men and 2 women whose ages ranged from 28 to 69 years. Peripheral blood eosinophilia was observed in 7 patients. The serum total bilirubin was elevated in all 9, the peak values varying from 1.9 to 25.3 mg. per 100 cc. The serum alkaline phosphatase reached its peak value at the time of the peak serum bilirubin, or within 11 days thereafter. Rises in the total lipids were observed in the 4 patients for whom this determination was available. The serum glutamic pyruvic transaminase was determined in 6 patients and was elevated in all of them. The serum glutamic oxalacetic transaminase was elevated in 4 of these and remained normal in 2. Liver enlargement was detected by palpation or by roentgenologic examination.

A total of 26 needle aspiration biopsies were performed, varying from 1 to 5 specimens per patient. Cholestasis was apparent in the earliest specimens as granules of bile pigment within cytoplasms of the centrolobular liver cells; later specimens showed distended canaliculi containing large, deeply stained masses of pigment. Some degree of portal fibrosis was found as early as the 25th day of illness and as late as 16 months after the onset. Unicellular liver-cell necrosis was found in significant extent in all 9 patients. Regeneration of liver cells was evident in the centrolobular zones of all the patients, while necrosis of interlobular bile ducts occurred in 2. The findings suggest that necrosis of liver cells (hepatitis) may play a more important role in the causation of chlorpromazine jaundice than is generally recognized. The disease is of prolonged duration histologically, although it has a transitory symptomatology. This duration is reflected in the laboratory measurements, particularly in the serum alkaline phosphatase and often in persisting eosinophilia. There was no evidence of the development of permanent residual damage or fibrosis in the liver in any of the 9 patients reported, although a transient portal fibrosis was observed after resolution of the portal infiltration. The necrosis and subsequent regeneration observed in 2 patients suggest the extension of a destructive process ordinarily limited to the intralobular cholangioles.

PHYSIOLOGY

A Study on the Possible Bronchodilating Effect of Corticotropin (ACTH) in the Therapy of Bronchial Asthma. E. Cerchiai. Minerva med. 50:3078-3084 (Sept. 29) 1959 (In Italian) [Turin, Italy].

The author reports an experimental study on the possible direct effect of corticotropin (ACTH) on the bronchial muscles of the isolated lungs of guinea pigs. The results of this study seem to warrant the hypothesis that the antiasthmatic effect of corticotropin may occur through a direct, pharmacodynamic effect of corticotropin itself, with the need of no other mediating factors, this effect being independent from the main hormonal function of the compound itself. This hypothesis was suggested by the observation that some asthmatic patients do not respond to cortisone, while they do respond to corticotropin. The effect of corticotropin on the lung after the administration of histamine and the effect of histamine after the administration of corticotropin were studied. A dose of 5 units of corticotropin dissolved in 2/10 cc. of isotonic sodium chloride solution was used. Corticotropin had a marked dilating effect on the lung in basal condition; this effect, however, took longer than the effect of ephedrine to become manifest. The degree and duration of the bronchodilatation were in proportion to the dosage of the drug used. Histamine, given 3 minutes after the administration of corticotropin, caused a bronchoconstriction which was gradual and delayed; this bronchoconstriction was less intense and lasted less than that observed when histamine was administered with the lung in basal condition. Different dosages of the 2 drugs caused quantitatively different effects. Corticotropin administered after histamine had a clear bronchospasmolytic effect, which was more delayed, however, than the effect obtained with ephedrine. The dosage used in this experiment did not cause a complete return to basal condition. Increasing the dose of corticotropin did not shorten the period of time necessary for the manifestation of the dilating effect; when the dilatation occurred, however, it was more marked than the dilatation obtained with the 5-unit dose.

The author believes that corticotropin may have a direct effect on the bronchial muscles without the need of mediating factors. Corticotropin manifests this direct effect when it causes the dilatation of a bronchus which has not undergone drug-provoked spasm and when it prevents the bronchoconstriction caused by histamine. The effect of corticotropin is not as rapid as that of ephedrine, and its intensity is proportional to the dose used. The author believes also that the spasmolytic effect of corticotropin, when given after the administration of histamine, does not occur through an antihistaminic mechanism, but is the result of the bronchodilating effect of corticotropin and of the bronchoconstricting effect of histamine.

Investigation of the "Diego" Blood Factor in a General Chilean Population and in Mapuche Indians. C. Meza Arrau, J. Staeding and A. Nijamkin. Rev. méd. Chile 87:690-692 (Sept.) 1959 (In Spanish) [Santiago].

The "Diego" blood antigen is found in the blood of persons having Mongolian ancestors. The antigen is serologically independent from all other known blood factors. It gives rise to a weak, incomplete, immune antibody which does not agglutinate the erythrocytes of normal blood. Frequently, although not always, it causes maternal-fetal incompatibility with production of erythroblastotic fetuses. The blood of the mothers, as well as that of the fetuses, reacts positively to the classical indirect Coombs test, in which the anti-Diego blood serum is used. The Diego blood factor has been previously identified among small groups of Caribbean Indians (29%), Brazilian Indians (45%), Inca Indians (25%), Chippewa Canadian Indians (10%), Chinese (5%), and Japanese (12%). Apparently all these groups are of Mongolian origin. This factor does not exist in the blood of Europeans, pure African Negroes, and pure American Indians. Its presence in the blood of American Indians is a proof of the Mongolian origin of those Indians, whereas its absence in the blood of certain groups of Indians shows pure American Indian ancestry.

The Diego factor was investigated in the blood of 120 Chileans and 100 Mapuche Indians of the O blood group. The parents of the Indians were 88 Indian couples and 12 couples consisting of an Indian and a mestizo. The classical indirect Coombs test was used. The test was positive in one person out of the 120 Chileans (0.8%) and in 4 Indians (4%). The Rh$_0$ Diego factor was positive in all 100 Indians. The authors conclude that the Diego factor is of value for determining the exact racial ancestry (Caucasian, Mongolian, or Negro) of a population and also for determining the Mongolian origin of American Indians, the test being positive only in persons with Mongolian ancesters.

BIOCHEMISTRY

Substances Released from the Skin Following Thermal Injury: "Burn Toxin." R. Rosenthal. Surgery 46:932-947 (Nov.) 1959 [St. Louis].

Rats were anesthetized with pentobarbital (Nembutal), and subcutaneous air pockets were made on their backs by injecting 30 cc. of air. The rats were held by their feet and immersed in a water bath at the desired temperature and for certain lengths of time. The burned animals were suspended by their feet, with the dorsal pockets down. Five cubic centimeters of triple-distilled water was injected into each pocket and gently shaken over the inner surface of the burned skin in such a way that the fluid came in contact only with the undersurface of the skin involved. After 5 minutes this water was removed, and another 5 cc. was injected into the pocket. This procedure was repeated 20 to 25 times over a period of 2 hours immediately after the burning of the skin. The fluid containing the diffusible materials from the burned skin was placed immediately in an ice bath, or was frozen by immersion of the container in a mixture of dry ice and alcohol. Diffusates were obtained by the same procedure from not burned rats. In more han 400 burned and not burned animals the av- rage yield of dry material perfused for 2 hours t 5-minute intervals was approximately 30 mg. er animal. The amount of material by dry weight vas similar in both groups.

The protein content and the protein nitrogen con- ent were the same in the lyophilized diffusates f both burned and not burned rats for the first our of collection, then increased appreciably in he burned sample during the second hour. The ost significant difference between the 2 samples as the higher content of potassium and phos- horus in the burned fluid. There was approxi- ately 1.2 to 1.4 mcg. per cubic centimeter of istamine in the crude dried material from the urn" perfusate. The lyophilized material was issolved in water or in a 0.9% sodium chloride lution and injected subcutaneously in small rats. qual volumes of 0.9% sodium chloride solution, ncentrated hemoglobin, or concentrated skin ex- acts were injected in control rats. Doses of 108 210 mg. of the "burn" diffusate solution caused rostration, marked decrease in activity, and diffi- lty in locomotion. Doses of 280 to 600 mg. caused eath within 5 hours. The average lethal dose, dministered subcutaneously, was approximately 7 mg. of the crude material per gram of body eight. The "burn" perfusate was also adminis- red in peritoneal, intravenous, and intracerebral jections.

The author affirms the existence of a "burn xin," originating in the skin proper and having unknown chemical composition. It is lethal to ice and rats in subcutaneous, intraperitoneal, travenous, or intracerebral injections, producing ute or chronic symptoms, depending on the dose d on the route of administration. Immunological udies showed that this toxin enters the circulation.

therosclerosis and Deficiency of Essential Fatty cids. H. Malmros and G. Wigand. Lancet 2:749-51 (Nov. 7) 1959 [London].

The authors report the results of dietary experi- ents made on rats in the department of clinical emistry of the University in Lund, Sweden. A misynthetic diet containing sugar, starch, cellu- se, casein, vitamins, and salts, but neither cho- sterol nor fat, induced hypercholesteremia and bsequent atherosclerosis in full-grown rabbits. part from hypercholesteremia, the animals did t show any clear signs of deficiency of essential tty acids. Hypercholesteremia disappeared when rn oil in a concentration of 8% was added to the eviously fat-free diet. The semisynthetic diet ith the addition of coconut fat or butter in con- ntrations of 8% also induced hypercholesteremia and atherosclerosis. The addition of glyceryl trilaurate in a concentration of 8% to the semisynthetic basic diet produced a considerable rise in the serum cholesterol level of the animals. This enhancing effect was diminished, though not completely abolished, by the addition of corn oil or pure linoleic acid in concentrations of 4%. This was probably due to a relative deficiency of essential fatty acids. There is much to suggest that the same nutritional-metabolic changes may occur in man on an unbalanced high-fat diet, and that atherosclerosis is thus a symptom of relative deficiency of essential fatty acids.

Peripheral Venous Blood Concentrations of Epinephrine and Norepinephrine in Primary Raynaud's Disease. J. H. Peacock. Circulation Res. 7:821-827 (Nov.) 1959 [New York].

The author performed chromatographic separation and biological assay of extracts from the peripheral venous blood of 9 women and 2 men, between the ages of 22 and 54 years, with primary Raynaud's disease, who had been admitted to the University Hospital in Ann Arbor, Mich. Of the 11 patients, 2 had clinically mild disease, 8 had moderately severe disease with pain being a dominant symptom, and 1 had severe disease with secondary ulceration of several digits. The results showed that the concentrations of epinephrine and of arterenol (norepinephrine) in the peripheral venous blood samples, obtained at the patient's wrist, were higher than normal when estimated by chromatography and biological assay under warm resting conditions. An increase, mainly of the arterenol fraction, which appeared to reflect the clinical severity of the condition, was observed in most patients after sympathetic nervous stimulation by cold. The high concentrations are considered to be due to an abnormal metabolism of these substances which probably arise mainly, if not entirely, from the peripheral sympathetic nerve endings.

The possible reasons for this abnormality are discussed, and it seems possible that the intense peripheral vasoconstriction and high concentration of vasoconstrictor substances seen in these patients could be related to the incomplete destruction of the amines liberated from the peripheral sympathetic nerve endings in the wall of the arteries of the hands and digits. This concept is supported by the findings in a finger amputated for terminal gangrene in a 22-year-old woman with Raynaud's disease. The proximal portions of 2 digital arteries were patent and microscopically normal, and no amine oxidase could be detected. In 2 other digital arteries taken from 2 digits amputated for nonvascular reasons, the amine oxidase activity was 552 microliter oxygen per gram per hour.

PUBLIC HEALTH

Lung Cancer Among White South Africans. G. Dean. Brit. M. J. 2:852-857 (Oct. 31) 1959 [London].

The author analyzed the deaths from lung cancer, occurring among white men in the Union of South Africa, by age, country of birth, and place of residence according to death certificates issued between 1947 and 1956. Results showed that among those dying between the ages of 45 and 64 years, but not among those dying at the age of 65 or over, the proportions of deaths from lung cancer were much higher among the British immigrants than among Union-born men or immigrants from other countries. Moreover, among all 3 categories of the white population in South Africa—Union-born men, British male immigrants, and male immigrants from other countries—the lung cancer mortality rates increased approximately with the level of urbanization and industrialization. Neither the differences between the lung cancer mortality rates of these 3 groups nor the urban/rural gradient can be attributed to differences in smoking habits. Instead, both would seem to have been due to the exposure of the men concerned to different degrees of atmospheric pollution. The excess lung cancer mortality among British immigrants dying under the age of 65, as compared with Union-born white men, would seem to have been due to their exposure in Britain to some form of atmospheric pollution to which those emigrating before 1910 had not been subject, since above that age there have been no significant differences between the lung cancer mortality rates in the 2 groups. The urban/rural lung cancer mortality gradient in South Africa would appear to reflect the increasing atmospheric pollution that is observed in passing from rural areas to areas of increasing industrialization.

Factors Affecting the Incidence and Severity of Poliomyelitis: An Analysis of the 1958 Epidemic in New Jersey. W. J. Dougherty and S. N. Faro. New England J. Med. 261:934-936 (Nov. 5) 1959 [Boston].

The 1958 epidemic of poliomyelitis in New Jersey accounted for 266 cases, an incidence rate of 5 per 100,000 population. Of these 266 patients, 186 had paralytic poliomyelitis and 80 the nonparalytic disease. Thirty-five per cent of the patients with paralytic symptoms were of preschool age. The incidence rate for paralytic poliomyelitis among nonwhites was 5 times that of the white population, and the incidence rate for nonparalytic poliomyelitis was 2.6 times that of the white population. Poliomyelitis in New Jersey in 1958 was essentially an illness of nonvaccinated persons. Of 186 patients with paralytic disease, 142 were unvaccinated, and of 80 patients with nonparalytic poliomyelitis, 39 were unvaccinated; 31 patients of the latter group, however, had received 3 inoculations of Salk vaccine. Poliomyelitis was confirmed by virus isolation in 119 of 149 patients with paralytic symptoms and in 13 of 58 patients with nonparalytic symptoms. Eight of the 266 patients died, 6 of them not having been vaccinated against the disease. One 11-year-old girl who died had received 3 inoculations, the third of which had been given in November, 1957. Among 178 patients with paralytic poliomyelitis, 155 had some residual paralysis on follow-up examination, and half of the patients who had not received Salk vaccine suffered moderate to severe residual involvement. The degree of residual involvement of 149 patients, on whom laboratory results have been obtained, does not appear to differ in infections due to type 1 and type 3 poliomyelitis virus.

Studies on an Outbreak of Echo Virus Infection in a Circumscribed Population. M. I. Goldenberg and M. Gudnadottir. Connecticut Med. 23:693-696 (Nov.) 1959 [New Haven].

A survey was conducted from Aug. 1 to Nov. 1, 1958, of a circumscribed population in New Haven, Conn., to determine the etiology, incidence, and symptomatology of enteric cytopathogenic human orphan (ECHO) virus infection. The study involved 120 (88%) of the families living in a housing development, with a total of 345 persons. There were 105 infants and children, ranging in age from 6 months to 12 years, and 240 adults, between the ages of 19 and 36 years. The study showed that 49 (23 infants and children, and 26 adults) of the 345 individuals had been ill with symptoms and signs suggestive of ECHO 9 virus infection. A different clinical picture was seen in the 2 age groups. The cardinal signs in infants and children were exanthema and fever, particularly among those ranging in age from 6 months to 4 years, whereas in adults the disease was more often characterized by meningeal symptoms, such as occipital headache and/or stiff neck. The disease was not severe enough in any of the patients to require hospitalization, and no lumbar punctures were made. Other symptoms, such as fever, anorexia, or nausea and gastrointestinal disturbances, were common in both groups. Stool samples obtained from 7 of the 49 individuals with varying degrees of illness were tested, and ECHO 9 virus was isolated from 4 specimens. It was possible to ascertain the date of onset of symptoms in 41 of the 49 persons studied. The data indicated that the peak incidence of diseases occurred in August and the first half of September; a smaller peak occurred in the first week of October.

BOOK REVIEWS

The Surgical Treatment of Facial Injuries. By Varaztad Hovhannes Kazanjian, C.M.G., D.M.D., M.D., Plastic Surgeon, Senior Active Staff, New England Deaconess Hospital, Boston, and John Marquis Converse, M.D., F.A.C.S., Lawrence D. Bell Professor of Plastic Surgery, New York University College of Medicine, New York. Second edition. Cloth. $22. Pp. 1110, with 1155 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2, 1959.

This revised textbook covers completely the subject of soft tissue and bone injuries of the face. The first four chapters cover the basic principles involved in repairing soft tissue defects and are well presented. Chapters 5 to 12 describe the treatment of facial bone fractures. Many will disagree with some of the corrective methods shown. Too much emphasis is placed on the use of cumbersome plaster of Paris headgear with various wires and levers attached. Most plastic surgeons consider this out of date and frequently ineffective. The same may be said of the use of external pin fixation. The use of various types of open reduction with wire and Kirschner pins is simpler and more accurate and is not accompanied by the numerous complications resulting from head cap and external pin techniques.

Roentgenographic demonstration of facial bone fractures is frequently difficult, but chapter 13 demonstrates these techniques unusually well. Chapters 15 to 19 discuss the transplantation of skin, mucosa, flaps, bone, and cartilage. These are good chapters and the techniques are accurately portrayed. One wonders, however (fig. 452), how many modern operating rooms stock sulfanilamide powder to aid in removal of a skin graft from the Padgett dermatome. The remaining chapters deal with the surgical reconstruction of specific parts of the face, scalp, eyelids, orbits, nose, and jaws. The treatment of facial paralysis is covered in a separate chapter.

The book is long but is filled with illustrations. It should find a useful place on the reference shelves of any large medical library. It would probably not be of interest to many plastic surgeons because it covers only a limited portion of their specialty. The publishers are to be complimented on the excellent printing and the fine reproduction of photographs, roentgenograms, and illustrations.

American Universities and Federal Research. By Charles V. Kidd. Foreword by Paul E. Klopsteg. Cloth. $6. Pp. 272. Belknap Press of Harvard University Press, Cambridge, Mass.; Oxford University Press, Amen House, Warwick Sq., London, E. C. 4, England, 1959.

Physicians will miss little if they are unable to find the time to read this book. Approaching the problem of the impact of federal research grants on the universities of America in a variety of ways, the book contains much repetition. It is characterized by equivocal conclusions. In brief, the author concludes that "the effects of federal research funds on universities cannot be determined objectively and precisely" (p. 208). He adds that cultural pressures affect government and universities and constitute the basic influencing force in our society. The nature of his conclusions is also revealed by such passages as: "University research in virtually all fields is more extensive, and in most fields of higher average quality, as a result of federal funds" (p. 211). This appraisal would hardly seem to comfort the taxpayer for the vast amount of funds expended and the detour via government his funds had to take to become available for research.

"Only 10% of university research," says Kidd, "is self-financed whereas more than 70% is financed by the federal government." It is not surprising therefore that "the central thesis of this book is that large-scale federal financing of research has set in motion irreversible forces that are affecting the nature of universities, altering their capacity to teach, changing their financial status, modifying the character of parts of the federal administrative structure, establishing new political relations, and changing the way research itself is organized" (p. v). Practically all of the conclusions constitute opinions which unfortunately cannot be tested by use of quantitative evidence.

Special attention is given to medical schools and federal funds because of problems of financing medical schools and because of medical schools' research programs. These programs have placed severe pressures on availability of medical school faculty and funds available for instruction. These conditions are especially serious since there are many people who believe that continued expansion of medical schools will be necessary. The author believes that if financing of medical education from private sources is not greatly increased, the universities will be forced to accept federal support for medical education as well as for medical research.

One difficulty with federal financing of university research, which the author notes, is that federal research funds may have attracted many faculty scientists away from their role of teaching. The relationship, however, between federal research funds and the decrease in the quality of instruction at universities may be as important as the relationship between federal funds and university research. A statistical appendix provides a brief summarization of the data used in this study.

Child Research in Psychopharmacology. Organized and edited by Seymour Fisher, Ph.D., Research Psychologist, Psychopharmacology Service Center, National Institute of Mental Health, U. S. Public Health Service, Bethesda, Md. With foreword by R. H. Felix, M.D., Director, National Institute of Mental Health. Cloth. $6.50. Pp. 216, with 7 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This volume is a report of a multidisciplinary conference that was intended to focus on short-term and long-term problems of drug effects. The primary objects of the conference were as follows: (1) to focus on basic short-term and long-term problems of drug effects on psychological functions, family relationships and community adjustment, maturational and developmental processes, and the central nervous system; on the type of child (i. e., disturbed, psychotic, or normal); and on research methodology and measuring instruments; (2) to develop new hypotheses and approaches to the study of drug-effects in children, taking into consideration historical background variables and personality differences; situational variables such as stress, motivation, rewards and punishments; and socio-environmental variables such as clinic, school, and family atmospheres; (3) to pave the way for initiating long-term developmental studies; and (4) to stimulate further interest in drug research with children.

Throughout the discussion, various contributors emphasized and reemphasized the possible effects of drug research on developmental aspects of the child. Contrast was made between children and adults, for investigative purposes. Of particular significance is the chapter by Sherman Ross on comparative drug behavior and the discussion that followed. The different effects of the same drug at different age levels in relation to the developmental problems are stressed. There is an excellent essay by Senn on the possible misuse of drugs as substitutes for adequate diagnosis and psychotherapeutic procedures. The volume has a valuable annotated reference list on the use of pharmacology for children, with a subject index which should be valuable to those interested in the field. This volume achieves its purpose as a report of a pioneering effort.

Anesthesia for Infants and Children. *By Robert M. Smith,* M.D., Anesthesiologist, Children's Medical Center, Boston. Foreword by Robert E. Gross, M.D. Cloth. $12. Pp. 418, with 182 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3; Henry Kimpton, 134 Great Portland St., London, W. 1, England, 1959.

"The purpose of this book is to assemble as much practical information as is available concerning the basic responses of children to anesthesia." The author writes from his own experience and knowledge and emphasizes the differential diagnosis and general principles and procedures of clinical management rather than detailed descriptions of specific techniques and complicated treatment. Emphasis is placed on information on pathology, pediatrics, and surgery, which the anesthetist usually lacks when called on to care for infants and children.

In each chapter are references which include only articles that have made definite contributions to the subject matter of the chapter. Bibliography and index are adequate. Of particular interest are the discussions of basic requirements in pediatric anesthesia, biology and behavior, hypothermic anesthesia for thoracic surgery, fluid therapy, and blood replacement. The excellent chapter on respiratory physiology was written by C. D. Cook. Fluothane is mentioned only briefly. More space could have been given to this timely subject.

This excellent book contains comprehensive review of clinical management of pediatric anesthesia. It stresses differential diagnosis and general principles and procedures rather than specific techniques and complicated treatments. It is well illustrated and should prove a welcome addition to the library of every anesthesiologist and student interested in anesthesia care of infants and children.

The Law of Medical Practice. By Burke Shartel, Professor of Law, University of Michigan, Ann Arbor, and Marcus L. Plant, Professor of Law, University of Michigan. Cloth. $12.50. Pp. 445. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This book deals with law as it may relate to or influence the practice of a physician as he conducts his professional activities. The authors express hope that the book will meet the daily need of established practitioners, offer medical students more than the bare minimum of medicolegal information needed to pass an examination for licensure, and aid lawyers who are called on to assist physicians in matters relating to medical practice. The authors have made wide use of medicolegal cases, abstracted by the American Medical Association's Law Division and published in THE JOURNAL. They rightly point out that so far no medicolegal book has made systematic use of this material.

The book represents an attempt to cover a wide field in one volume. The subject is comprehensive because, in medical practice, sooner or later, almost every problem known to law may be encountered. A major criticism of this work might be that an attempt has been made to cover too much, as a book could be written about the subject of each chapter. The authors, however, deserve credit for bringing many medicolegal discussions together.

An indication of the scope of the book is its eight chapters entitled The Physician's Professional Services, Compensation for Medical Care, The Physician's Liability for Medical Care, Other Tort Liability Incident to Medical Practice, Licensure of Physicians and Other Practitioners of the Healing

Art, The Physician's Business Transactions and Relationships, The Physician's Public Duties and Liabilities, and Operation of the Legal System: General View. Each chapter is practical, well written, and well documented. The authors do not write abstractly or from the strictly legal point of view. Examples and illustrations demonstrate the rule or point under discussion.

No physician could be expected to read this book from cover to cover. He could, however, refer to it for general information to guide him in making his decisions or to encourage him to seek advice from his attorney in other situations. The book could be used by medical students who wish to enter practice with some knowledge of the effect that statutes and court decisions have on the conduct of their profession. Lawyers who are called on from time to time to advise physicians may expect this book to furnish helpful perspectives to medicolegal issues and to furnish leads to reported court cases and existing statutes related to the issue under consideration.

This book is a contribution to the medicolegal literature and may be recommended to the physician or medical student as an acceptable exposition of the law as it affects the practice of medicine.

Klinik und Praxis der Urologie: Klinik, Indikation, Diagnostik, operative und instrumentelle Eingriffe, Nachbehandlung. [In zwei Banden.] Band I. Von Prof. Dr. Werner Staehler. Mit einem Geleitwort von Prof. Dr. Th. Naegeli. Cloth. 240 marks; $57.15. Pp. 892, with 1034 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

Klinik und Praxis der Urologie: Klinik, Indikation, Diagnostik, operative und instrumentelle Eingriffe Nachbehandlung. Band II. Von Prof. Dr. Werner Staehler. Mit Namen- und Sachverzeichnis für Band I und II. Cloth. 240 marks; $57.15. Pp. 893-1755, with 641 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

Each of these volumes presents a vast amount of information on urology. The photographs and drawings, with their legends, are storehouses of information.

Volume 1 is an orderly presentation of historic developments of urology. Malformations are discussed, and the embryology of the urogenital system is described. Modern concepts of therapy and dangers encountered with antibiotics are presented, and infections occurring in various parts of the urinary tract are discussed. Urinary calculus, urinary retention, prostatic hypertrophy, cancer of the prostate, bladder neck contractures, and tumors of the kidney are described, and their sequela and treatment are discussed. At the end of each chapter is an excellent summary.

Volume 2 discusses anuria and its treatment and indications for dialysis, nephritis, hypertension, hematuria, stenosis of the renal artery, trauma to urinary tract, foreign bodies, parasitic disease, and disturbances in genital function of the male such as infertility, impotence, and climacteric.

The final chapter deals with physical examinations, laboratory tests, cystoscopy, surgical techniques, kidney transplantations, and operative and postoperative complications. These volumes are classics and should be read by all urologists.

Medical Discoveries: Who and When. By J. E. Schmidt, Ph.B.S., M.D., Litt.D. Dictionary listing thousands of medical and related scientific discoveries in alphabetical order, giving in each case name of discoverer, his profession, nationality, and floruit, and date of discovery. Cloth. $14.75. Pp. 555. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This collection of useful information lists more than 6,000 discoveries in medicine and related fields of science. Arranged by subject in encyclopedic style, each brief entry includes the name of the discoverer or inventor, some biographical data, and eponyms or synonyms for the subject. It is current enough to include information about the Salk vaccine. An introductory chapter explains the arrangement in some detail and offers suggestions as to how to locate desirable information.

One drawback to its use as a quick-reference tool is a lack of entries under proper names. For instance, the Salk vaccine entry is listed under "Poliomyelitis Vaccine, introduction of." Thus it offers little help in learning what a person did (unless there is an eponymic or syndromal type of entry, such as Hodgkin's disease), but it is an excellent source of information for facts on first accounts of various operations, anatomic discoveries, and diseases.

This book can be recommended as an excellent reference work on medical history. It is useful to the practicing physician as well as to the librarian or student of medicine or science. It is certainly a much-needed supplement to the existing reference books of its kind, such as Kelley's Encyclopedia of Medical Sources, which it somewhat resembles.

Diagnosis of Congenital Heart Disease: A Clinical and Technical Study by the Cardiologic Team of the Pediatric Clinic, Karolinska, Sjukhuset, Stockholm. By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe, and Bengt Jonsson. Second edition. Cloth. $28. Pp. 866, with 727 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1959.

This is the second edition of a work that is already a classic and standard reference in the field. The first edition, published in 1955, was based on 396 cases of congenital heart disease, and the case material has now nearly doubled in amount. The presentation is outstanding in respect to the angiocardiographic analysis. These detailed studies are clearly presented, and the radiographic reproductions represent a definitive atlas of congenital heart disease. The value of the radiographic material is enhanced by an abundance of carefully correlated postmortem illustrations.

The authors first present a concise embryologic survey of the circulatory system. The second chapter is an invaluable discussion of the anatomic and physiological features that are considered to be of importance for angiocardiographic interpretation. Special technical aids such as cardiac catheterization, angiocardiography, roentgenography, electrokymography, and phonocardiography, which make possible a detailed functional and anatomic diagnosis, are next presented in adequate detail. Separate chapters are devoted to a detailed presentation of clinical and laboratory diagnoses of major cardiovascular defects. Although this volume is not to be considered a textbook of general pediatric cardiology since there is little about the clinical course on therapy of congenital heart disease, it represents an outstanding and indispensable volume for all those interested in this subject.

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When this book first appeared in German, it met with immediate success. The English translation is therefore most welcome. It contains 99 color plates of excellent quality and good size so that details of lesions are easy to see. The black and white illustrations are well selected. The text is brief, yet adequate, and the suggestions for treatment are standard, practical, and current. The emphasis is on the more commonly encountered diseases with a view to meeting the needs of nondermatological specialists, general practitioners, and students. The book is well indexed and has an excellent list of references.

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The information in this cookbook can be of value to the patient who is advised to maintain a specific intake of fat. A wide variety of recipes is included, and the fat content has been calculated for each one.

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ESTIONS AND ANSWERS

LACERATIONS

edicament should a boxing when a fighter suffers a cut on the face?

James M. Willett, M.D., Elizabethton, Tenn.

Answer.—The ideal medicament to be applied, during a bout, to a laceration on the face of a fighter has long been the subject of controversy among physicians and trainers. To be ideal a medicament would have to be satisfactory for both the immediate and the later care of the wound, such as a topically applied lotion or ointment which effects rapid hemostasis and has no deleterious effect on the wound. Various solutions (Monsell's, ferric chloride, and epinephrine), pastes, and ointments (bismuth subgallate, zinc oxide, tannic acid, and carpenter's glues) are still being used at the ringside, a practice which should be condemned.

Topically applied thrombin or any of the approved thromboplastic substances appear to be the most effective coagulants and least injurious to the wound. Sterile petroleum jelly can be used but should be removed as soon as the fight is finished. Ice or water compresses may be effective adjunctive measures.

FUNGICIDAL ACTION OF ALCOHOL

To the Editor:—*Before a specimen is taken for culture of a suspected mycotic organism, the skin area from which it is taken is commonly cleansed with a 70% solution of ethyl alcohol. This practice apparently is based on the assumption that alcohol has no lethal effect on fungus growths. I wish to know whether or not this assumption has been challenged by experimental evidence?*

Kurt Loewenthal, M.D., Freeport, N. Y.

Answer.—There are few reliable documented data on the fungicidal action of ethyl or isopropyl alcohol. Textbooks and reviews occasionally state that alcohol is not an efficient fungicide, but the meager observations which have been recorded suggest that this is not the case. Spaulding (*Surg. Gynec. & Obst.* 69:738 [Dec.] 1939) asserted that Candida albicans organisms were rapidly killed by alcohol, even though embedded in blood or in pus on knife blades. With respect to the ringworm fungi, Emmons (*Arch. Dermat. & Syph.* 28:15 [July] 1933) noted that 80% alcohol destroyed the spores of Trichophyton, a ringworm fungus, within 30 minutes. Whether or not a shorter exposure time would also be lethal is not stated.

In view of the increasing recognition of ethyl and isopropyl alcohol as superior degerming agents, it seems wise to assume that fungi, especially the hyphal elements, are susceptible to alcohol. Cleansing of the lesion with soap and water would be a better way to decontaminate lesions prior to the collection of material for culture.

GRANULOSA CELL CARCINOMA

To the Editor:—*A 21-year-old woman has a granulosa cell carcinoma of the ovary which was incompletely removed. She is scheduled to hav therapeutic irradiation for this tumor, and he attending physician raised the question whethe administration of testosterone would inhibit th growth of the tumor. The patient has symptom of hyperestrogen effect. What should be done?*

M.D., Oregon.

Answer.—It is mandatory, if the tumor is ope able, that a second operation be performed. Thes tumors are radiosensitive, but, if irradiation is uti ized, the other ovary will also be damaged an the patient's normal physiology will be altered. If, the time of the first operation, the primary tum was confined to one ovary, unilateral oophorectom will suffice and the remaining ovary, if found fre of disease, will remain so for a number of year During this time the patient could, if married, be several children before hysterectomy and ooph rectomy become necessary. When all of the tum tissue is removed, her hyperestrogenism will disa pear. The only use of androgen therapy would b to hasten this change. There is no information whic suggests that administration of androgens wi destroy a granulosa cell tumor or enhance oth therapeutic measures used to overcome it.

SNORING SOUNDS DUE TO PARALYSIS AGITANS

To the Editor:—*Is there any way to control th moaning expiratory noise emitted by an elder patient with paralysis agitans (Parkinson's di ease) due to arteriosclerosis? The noise is made i voluntarily and occurs frequently while she sleeping; when she is awake, she can stop th sound if it is brought to her attention.*

Morton J. Silk, M.D., Morris Plains, N. J.

Answer.—Snoring of this nature is exceeding difficult to control, and nothing other than perform ance of a tracheotomy will stop it. If it is disturbin to someone nearby, the simplest remedy would b for either person to sleep in another room. Encou aging the patient to sleep on her side rather than o her back may help, but this might be difficult f her to do. Administration of sedatives usually a gravates rather than helps this condition.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

WASHINGTON NEWS

White House Aging Conference . .
Warning Label Bill Cleared . .
Air Pollution Bill Proposed . .
Drug Investigation . .
Radiation Limit Cut . .

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WARNS AGAINST HASTY ACTION ON AGED-HEALTH BILLS

The top Republican on the House Ways and Means Committee urged Congress to hold off action on legislation to provide health care of the aged before next year's White House Conference on Aging makes its recommendations.

Rep. Noah M. Mason (R., Ill.) charged that "certain organizations" are bringing pressure on Congress to act on such measures this year "without the benefits of adequate study and investigation" of the problems of older persons.

He declared Congress had considered the problems of the aged "so vast and so complicated as to require a White House Conference at a large expenditure of effort and funds."

Rep. Mason made public an exchange of correspondence with former Rep. Robert W. Kean (R., N. J.), Chairman of the National Advisory Committee supervising preparations for the White House Conference in January, 1961.

Representative Mason had written Kean for information for the House Ways and Means Committee on preparations for the White House Conference. The Committee was scheduled to start March 14 considering Social Security legislation, including a controversial bill introduced by Rep. Aime Forand (D., R. I.) that would provide hospitalization, surgical services, and nursing home care for social security beneficiaries through an increase in social security taxes.

Kean said he believed that "in all probability" most of the White House Conference's recommendations "will be for state and local activity." He said state and local action "seems most effective" in dealing with problems of older persons. However, he added that "certainly some suggestions as to additional executive and legislative level may be included" in recommendations of the conference, which will be held here next January.

Kean reported that the White House Conference of 2,800 delegates and the preliminary state and local conferences would cost the federal government about 2 million dollars. He outlined the extensive activities of his advisory Committee and said most states have scheduled their conferences.

Kean expressed hope "that in every activity the conference will be truly nonpartisan." He pointed out that Democrats controlled Congress when the law was passed in 1958 and that it is being carried out under a Republican Administration.

Meanwhile, three officials of the American Medical Association met with Arthur S. Flemming, Secretary of Health, Education, and Welfare to discuss the Forand bill situation. After the meeting, attended by Dr. F. J. L. Blasingame, A. M. A. Executive Vice-president, Dr. Julian Price, member of the A. M. A. Board of Trustees, and Dr. David Allman, past-president of the A. M. A., Flemming told a news conference that he had invited the A. M. A. representatives to talk over their ideas on the problem of health care of the aged, particularly in the area of catastrophic coverage.

Flemming disclosed that insurance and hospital representatives would also be called on for their views. He said the administration was exploring various possibilities as alternatives to the Forand bill. These would be in the areas of social security, public assistance, or some form of supplementary private insurance, he said.

COMMITTEE CLEARS WARNING LABEL BILL

The Senate Commerce Committee approved legislation endorsed by the American Medical Association to require the precautionary labeling of hazardous substances such as certain household products not now covered by federal regulations.

The bill, also supported by the administration, would replace existing statutes and provide more encompassing coverage of products requiring labeling. In addition, more detailed labeling would be required for flammable as well as potentially poisonous products.

The committee rejected suggestions, opposed by the A. M. A., to weaken the bill by omitting toxicological tests in determining the necessity of the word "danger" on products and applying the term only to very toxic substances, which also would be labeled "poison."

Commenting on the bill, HEW Secretary Flemming said, "There is wide agreement that present legislation in this field . . . has been greatly outmoded by the rapid increase in the number of chemical compounds available for household use. The 1927 act has helped to save many lives, but it is not applicable to many poisons and other hazardous substances and devices that are being used in homes today in ever-increasing numbers.

"A number of ordinary household materials, when swallowed, are poisonous and can cause death.

(Continued on next page)

Frequently—and often because parents are not aware of their danger—they are placed within easy reach of small children. These include paint and paint thinners and removers, cleaning agents, furniture waxes and polishes, bleaches, detergents, lighter fluids, and, of course, drugs and sometimes cosmetics."

ADMINISTRATION SUBMITS AIR POLLUTION BILL

The administration, with bipartisan backing, sent Congress a new program for expanding the government's efforts to attack the problem of air pollution in metropolitan areas.

The bill, introduced by Senators Thomas Kuchel (R., Calif.), Clair Engle (D., Calif.), Hugh Scott (R., Pa.), and Joseph Clark (D., Pa.), would make the present temporary air pollution control program permanent and give the Public Health Service stronger powers.

Under it, PHS would be authorized to hold public hearings on air pollution problems which are interstate in nature or of broad significance, and the 5-million-dollar ceiling on appropriations for the program would be eliminated.

In submitting the bill, Arthur S. Flemming, Secretary of Health, Education, and Welfare, declared, "Increasing evidence has accumulated of a causative relationship between air pollution and the incidence of respiratory chronic disease conditions. Further studies are urgently needed to investigate more fully these relationships and delineate practical procedures applicable in air pollution control practice."

"Continuing research and control efforts will be necessary if major adverse effects on the public health and welfare are to be prevented," he declared.

DRUG HEARINGS CALLED OFF TEMPORARILY

Sen. Estes Kefauver (D., Tenn.) indefinitely postponed hearings of his Senate antitrust subcommittee on drug industry practices, because of the lengthy civil rights debate on the Senate floor. In making the move after several postmidnight sessions, Kefauver said he hoped physicians would give serious thought to writing prescriptions by the generic or scientific term rather than the trade name.

At the abbreviated hearings, spokesmen for the drug industry took issue with the Senator's suggestion. Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association, said that in the first place prescribing by generic terms would not necessarily mean any savings for the patient. Furthermore, he said, "behind brand names lie the reputation, reliability, and skill of the manufacturer. Any system to substitute generic term for trade names also would restrict the physician's choice and transfer some of his responsibility to the

thorities. ist."
or other organi
mous communication
the writer's name and ad

"By brand name prescription, too, the doct orders for a patient a specific product in which h has absolute knowledge of quality, purity, and an side-effects that might have importance for a pa ticular patient," he testified. "In the case of combi nation formulations, brand names stand not onl for the active ingredient or ingredients but also fo special excipients, vehicles, and bases, frequentl developed by costly research to be nonallergeni specially buffered to promote tolerance, sugar-fre for the obese and diabetic, and many other impor tant variations for individual patient needs. So called generic equivalents often do not."

The wind-up witnesses were Drs. Haskell J Weinstein and Martin Seidell, who once worked fo Charles Pfizer & Co. They said that sometime there were conflicts between the marketing depart ments and the medical departments of drug com panies as far as drug advertising and promotio were concerned. In a statement, Pfizer flatly denie the charge.

When the hearings resume, spokesmen for th American Medical Association were expected t present to the lawmakers a rundown on how th A. M. A. carefully screens advertising in its journal

RADIATION LIMIT LOWERED BY GOVERNMENT

The maximum permissible "safe" radiation limi as gauged by the federal government, was sharpl reduced in a move that was described as purel precautionary. The limit, based on a lifetime e posure, was slashed for radioactive strontiu (Sr^{90})—one of the most dangerous and commo byproducts of nuclear fall-out—from 80 μμc to 3 μμc. The move was made shortly after an ad ho committee of the semiofficial National Committe on Radiation Protection and Measurements recom mended a lowering of permissible ceilings to on fifth of the existing national standards.

Arthur S. Flemming, Secretary of Health, Educa tion, and Welfare, said the government would im mediately use the reduced standards in its testin of levels of radioactivity on air, water, milk, an other products. Actually, radioactivity levels hav been dropping generally since the cessation by th United States and Russia of nuclear test explosion Only a few of thousands of samples have exceede the permissible ceilings, and these were unusua cases due in large part to location near plants pro ducing radioactive materials. The government ha repeatedly stressed that as far as can be ascertaine at the present time there is no danger to the popu lace from radioactivity levels.

Flemming said much more research needs to b done before scientists understand fully the bio logical effects of radiation on human beings. Notin that there has always been a certain amount o background radiation from natural sources, he sai that the lower limit is an attempt to peg radiatio safety levels more realistically to natural radiation The new standard, he said, would have little or n practical effect on the government's testing pro grams.

Advertisement

Pro-Banthīne®...what it will do and what it will not do...in Peptic Ulcer

uch consideration has been devoted ently to a reappraisal of the role of ticholinergic drugs in the manage- nt of peptic ulcer.

uch reappraisal has presented no dif- lties at Searle. At no time have we gested that Pro-Banthīne should be stituted for antacids, rest, psycho- rapy or even common sense in man- g the patient with peptic ulcer.

tion of Pro-Banthīne:

action of Pro-Banthīne (brand of pantheline bromide) is simple and its cts, allowing for the variability of the nan estate, are predictable. Pro- thīne competes with and, in compet- inhibits the action of acetylcholine. competition is highly effective at sympathetic effector sites and, ex- t with high dosage, somewhat less so e autonomic ganglia.

ince parasympathetic nerves are mo- and secretory to the stomach and or to the intestines, Pro-Banthīne re- es both motility and secretions in the ach and motility in the intestines. se actions have often been demon- ted experimentally and clinically.

at It Does:

eves Pain—One of the natural con- ences of the actions of Pro-Banthīne reduce or to eliminate pain in pep- lcer. Whether the pain is attributa- to acid, to excessive motility or, to r a middle course, to spasm induced cid, the pronounced inhibitory effect ro-Banthīne on both secretion and ility might be expected to suppress characteristic distress of ulcer.

point of fact, relief of pain is one he most prominent effects of Pro- thīne in peptic ulcer. Phrases such as xcelled" and "almost invariably ef- ive" dot the literature referring to it.

uces **Acidity**—Since reduction of and rest for the hypermotile stom- and duodenum are accepted means upporting the regenerative processes e gastroduodenal mucosa, the phys- gic modifications induced by Pro- thīne should be expected to have apeutic implications in the healing lcers also. They do. Not only does -Banthīne reduce gastric acid and ility but, through these actions, it potentiates and prolongs the neu- izing property of antacids.

s Healing—Schwartz, Lehman, Os- e and Seibel prescribed 120 to 180 of Pro-Banthīne daily for 129 ulcer ients and found definite evidence, both clinical and roentgenographic, of accelerated healing.

With high doses (270 to 330 mg. daily) Barowsky, Schwartz and Lister reduced the mean duration of treatment in twenty-five patients with refractory ulcers from 135 to 17 days.

Helps Prevent Recurrences—Much the same considerations argue for the value of Pro-Banthīne in holding the reactivation of healed ulcers in abeyance, but the difficulty of regulating the diet, medication and mode of living of ulcer patients over long periods of time makes assessment of the role of Pro-Banthīne in preventing recurrences difficult. Nevertheless, in a study of 250 patients with established patterns of recurrence Texter and associates found that patients maintained on methantheline, less potent analogue of Pro-Banthīne, had significantly fewer recurrences than a control series taking atropine.

Schwartz and his co-workers considered freedom from symptoms when recurrences would be expected, together with tolerance and relief of symptoms, as a standard in establishing successful treatment in 118 of 129 patients.

Provides Selective Action—In inhibiting the action of acetylcholine in the stomach and intestines Pro-Banthīne also, though to a lesser extent, influences other cholinergically activated organs. That this influence sometimes leads to such secondary effects as dryness of the mouth, blurring of vision and hesitancy of urination is well known and bears consideration. It is one of the distinct advantages of Pro-Banthīne that it acts more effectively on the gastrointestinal tract than elsewhere. Secondary effects usually disappear during the course of treatment and only rarely limit therapy.

Evidence of selective action has been recorded by several investigators, but the most interesting confirmation of this selectivity was reported by Barowsky, Schwartz and Lister. They prescribed 30 to 45 mg. of Pro-Banthīne every hour and a half, except for the hour before and the hour following meals, for their patients with refractory ulcers. They were surprised and gratified by how few anticipated side reactions materialized. No serious toxic effects or side reactions occurred. The incidence of good response on double or triple the usual doses rose from 31 to 88 per cent.

Lowers Incidence of Failures—Variable results might be anticipated in a disease in which the psychic component plays such a large part and, of course, response to treatment does vary in patients with peptic ulcer. Observations of Lichstein and associates show that the 11 per cent of their patients who failed to respond to Pro-Banthīne had deeply ingrained anxiety on a psychoneurotic basis.

Successful management of such patients may well depend more on the patient's intelligence, the modification of his social environment and the skill of his physician in psychotherapy than on any medication. However, the successful experience of Barowsky and his colleagues in using large, frequent doses of Pro-Banthīne in patients with refractory ulcers might be borne in mind before Pro-Banthīne is abandoned as ineffective. Also worthy of trial in these patients is Pro-Banthīne® with Dartal® (brand of propantheline bromide with thiopropazate dihydrochloride), which combines the outstanding anticholinergic action of Pro-Banthīne with the highly efficient tranquilizing action of Dartal.

What It Will Not Do:

There are aspects of the medical management of peptic ulcer in which Pro-Banthīne has no demonstrable benefit. There is no reliable evidence that Pro-Banthīne reduces the incidence of complications or the need for surgery.

It will not abolish the obligation of physicians to evaluate each patient individually and to modify therapeutic measures to each patient's requirements. Nor will it do away with the necessity for the patient to regulate his life to the demands of his disease. But the modifying action of Pro-Banthīne on the physiologic activity of the gastrointestinal tract and its beneficial effects on the course of peptic ulcer have been established by too many investigators to be seriously questioned. Wisely used in conjunction with other standard therapeutic measures, Pro-Banthīne can inhibit pain, hasten healing and space out the intervals of peptic ulcer recurrence and do so without serious discomfort to the patient.

G. D. Searle & Co., Chicago 80, Illinois. Research in the Service of Medicine.

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MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.
1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, *Washington, D. C., Nov. 28-Dec. 2.*
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-Dec. 1.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 25-30.

AMERICAN

1960

March

American Academy of General Practice, Philadelphia, Mar. 18-24. Mr. Mac F. Cahal, Volker Blvd., at Brookside, Kansas City 12, Mo., Executive Director.

American Association for the History of Medicine, Inc., Charleston, S. C., Mar. 24-26. John B. Blake, Ph.D., c/o Smithsonian Institution, Washington 25, D. C., Secretary.

American Broncho-Esophagological Association, Deauville Hotel, Miami Beach, Fla., Mar. 15-16. Dr. F. Johnson Putney, 1712 Locust St., Philadelphia 3, Secretary.

American College of Surgeons, Sectional Meeting, The Broadmoor, Colorado Springs, Colo., Mar. 21-23. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Sheraton-Portland Hotel, Portland, Ore., Mar. 28-30. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Gastroenterological Association, Roosevelt Hotel, New Orleans, Mar. 31-Apr. 2. Dr. Wade Volwiler, Dept. of Med., Univ. of Washington, Seattle, Secretary.

American Gastroscopic Society, Roosevelt Hotel, New Orleans, Mar. 30. Dr. Arthur M. Olsen, Mayo Clinic, Rochester, Minn., Secretary-Treasurer.

American Laryngological Association, Deauville Hotel, Miami Beach, Fla., Mar. 18-19. Dr. Lyman Richards, Massachusetts Institute of Technology, Cambridge 39, Mass., Secretary.

American Laryngological, Rhinological and Otological Society, Inc., Deauville Hotel, Miami Beach, Fla., Mar. 15-17. Dr. C. Stewart Nash, 708 Medical Arts Bldg., Rochester 7, N. Y., Secretary.

American Otological Society, Deauville Hotel, Miami Beach, Fla., Mar. 13-14. Dr. Lawrence R. Boies, University Hospital, Minneapolis 14, Minn., Executive Secretary-Treasurer.

American Otorhinologic Society for Plastic Surgery, Inc., Deauville Hotel, Miami Beach, Fla., Mar. 6-13. Dr. Joseph G. Gilbert, 75 Barberry Lane, Roslyn Heights, N. Y., Secretary.

American Psychosomatic Society, Sheraton-Mount Royal Hotel, Montreal, Mar. 26-27. Miss Joan K. Erpf, 265 Nassau Rd., Roosevelt, N. Y., Executive Assistant.

American Radium Society, Caribe Hilton Hotel, San Juan, Puerto Rico, Mar. 17-19. Dr. Robert L. Brown, Robert Winship Clinic, Emory University, Atlanta 22, Ga., Secretary.

American Society of Maxillofacial Surgeons, Ambassador Hotel, Los Angeles, Mar. 27-30. Dr. E. M. Collins, Christie Clinic, Champaign, Ill. Public Relations Committee.

Intermountain Pediatric Society, *Stardust Hotel, Las Vegas, Nev.,* Mar. 28-29. Dr. Joseph R. Newton, 2000 S. 9th East, Salt Lake City, Utah, Publicity Chairman.

Missouri State Medical Association, Sheraton-Jefferson Hotel, St. Louis, Mar. 13-16. Mr. T. R. O'Brien, 634 N. Grand Blvd., St. Louis 3, Executive Secretary.

National Health Council, National Health Forum, Miami, Fla., Mar. 13-18. Mr. Philip E. Ryan, 1790 Broadway, New York 19, Executive Director.

Neurosurgical Society of America, Del Monte Lodge, Calif., Mar. 30-Apr. 2. Dr. Raymond K. Thompson, 803 Cathedral St., Baltimore 1, Secretary.

Southeastern Surgical Congress, Roosevelt Hotel, New Orleans, Mar. 21-24. Dr. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga., Executive Secretary.

Southwestern Society for Nuclear Medicine, Menger Hotel, San Antonio, Texas, Mar. 26-27. Dr. J. R. Maxfield Jr., 2711 Oak Lawn Ave., Dallas 19, Secretary.

Southwestern Surgical Congress, Riviera Hotel, Las Vegas, Nev., Mar. 28-31. Miss Mary O'Leary, 1213 Medical Arts Bldg., Oklahoma City, Okla., Executive Secretary.

April

Alabama, Medical Association of the State of, Admiral Semmes Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery 4, Executive Secretary.

American Academy of Neurology, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

American Association for the Advancement of Science, Section on Medical Sciences, Vanderbilt University, Apr. 18-19. Dr. George R. Meneely, Vanderbilt University School of Medicine, Nashville 5, Tenn., Chairman.

American Association of Anatomists, Statler-Hilton, New York C Apr. 11-16. Dr. Louis B. Flexner, Dept. of Anatomy, School of Medic *Univ. of Pa., Philadelphia 4, Secretary-Treasurer.*

American Association of Immunologists, Chicago, Apr. 11-15. Calderon Howe, Columbia Univ. College of Physicians and Surge New York 22, Secretary-Treasurer.

American Association of Pathologists and Bacteriologists, H Peabody, Memphis, Tenn., Apr. 28-30. Dr. Russell L. Holman, D of Pathology, L. S. U. School of Medicine, New Orleans, La., Secret

American Association of Railway Surgeons, Drake Hotel, Chic *Apr. 7-9. Mr. Chester C. Guy, 5800 Stony Island Ave.,* Chicago Executive *Secretary.*

American College Health Association, Toronto, Canada, Apr. 27- Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. *Secretary-Treasurer.*

American College of Obstetricians and Gynecologists, Nether Hilton Hotel, Cincinnati, Apr. 2-6. Mr. Donald F. Richardson, 79 Monroe St., Chicago 3, Executive Secretary.

American College of Physicians, *Mark Hopkins & Fairmont,* San F cisco, Apr. 4-9. Dr. Edward C. Rosenow Jr., 4200 Pine St., Philadel 4, Executive Director.

American College of Surgeons, Sectional Meeting, Hotel Leamin *Minneapolis,* Apr. 11-13. *For information write: Dr. H. P.* Saun 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Kahler H Rochester, Minn., Apr. 14. *For information write:* Dr. H. P. Saun 40 *E. Erie St., Chicago 11.*

American College of Surgeons, West Virginia Chapter, The Gr brier, White Sulphur Springs, W. Va., Apr. 1-2. Dr. Ray E. Bu *Grace Hospital, Welch, W. Va., Vice-President.*

American Dermatological Association, Inc., *Boca Raton Hotel,* B Raton, Fla., Apr. 8-12. Dr. Wiley M. Sams, 308 Ingraham Bldg., M 32, Fla., Secretary.

American Physiological Society, Chicago, Apr. 11-15. Ray G. D *D.Sc.,* 9650 Wisconsin Ave., Washington 14, D. C., Executive Secret

American Proctologic Society, Shamrock Hilton Hotel, Houston, Te Apr. 25-27. Dr. Norman D. Nigro, 10 Peterboro, Detroit 1, Secret

American Public Health Association, *Southern Branch,* Mem Tenn., Apr. 13-15. *Dr. L. M. Graves, Shelby County* Health Dep ment, Memphis, Tenn., Chairman, Local Arrangements Committe

American Society for Artificial Internal Organs, Pick-Cong Hotel, Chicago, Apr. 10-11. Dr. Charles K. Kirby, 3400 Spruce *Philadelphia 4.*

American Society of Biological Chemists, Inc., Chicago, Apr. 11 Dr. Frank W. Putnam, Dept. *of Biochemistry,* Univ. of Florida, Gai ville, Secretary.

American Society for Experimental Pathology, *Pick-Congress* H Chicago, Apr. 11-15. Dr. J. F. A. McManus, Univ. of Alabama M Center, Birmingham, Ala., Executive Secretary.

American Society of Facial Plastic Surgery, Hotel Elysee, New Y City, Apr. 6. Dr. Samuel M. Bloom, 123 E. 83d St., New *York* Secretary.

American Society of Internal Medicine, Sheraton-Palace *Hotel,* Francisco, Apr. 1-3. Mr. Robert L. Richards, 350 Post St., San Franc 8, Executive Director.

American Society for Pharmacology and Experimental The peutics, Inc., Chicago, Apr. Dr. Karl H. Beyer Jr., *Merck Sharp* Dohme Research Labs., West Point, Pa., Secretary.

American Society for the Study of Sterility, *Sheraton-Gibson* H Cincinnati, Apr. 1-3. Dr. Herbert H. Thomas, 920 S. 19th St., Birmi ham 5, Ala., Executive Secretary.

American Surgical Association, The Greenbrier, White Sulphur Spri W. Va., Apr. 3-6. Dr. W. A. Altemeier, *Cincinnati General* Hospi Cincinnati 29, Secretary.

Andrew, John A., Clinical Society, Tuskegee Institute, Alaba Apr. 24-29. Dr. Eugene H. Dibble, Memorial Hospital, Tuskegee In tute, Ala., Secretary.

Arkansas Medical Society, Pine Bluff, Apr. 18-20. Mr. Paul C. Schae 218 Kelley Bldg., Fort Smith, Ark., Executive Secretary.

Connecticut State Medical Society, Hamden High School, Hamd Apr. 26-28. Dr. William R. Richards, 160 St. Ronan St., New Hav Conn., Secretary.

Florida Medical Association, Robert Meyer Hotel, *Jacksonville,* A 8-12. Mr. W. Harold Parham, 735 Riverside Ave., Jacksonville 3, F Executive Director.

Harvey Cushing Society, Fairmont Hotel, San Francisco, Apr. 13- Dr. Edmond J. Morrisey, 450 Sutter St., San Francisco, Chairman

Industrial Medical Association, Rochester, N. Y., Apr. 26-29. *Clark D. Bridges, 28 E. Jackson Blvd., Chicago 4,* Managing Direc

Iowa State Medical Society, Savery Hotel, *Des Moines,* Apr. 24- Mr. Donald L. Taylor, 529 36th St., *Des Moines* 12, Iowa, Execut Director.

Maryland, Medical and Chirurgical Faculty *of the* State of, T Alcazar, Baltimore, Apr. 20-22. Mr. John Sargeant, 1211 Cathedral S Baltimore 1, Executive Secretary.

Mid-Central States Orthopaedic Society, Wichita, Kan., Apr. 8- Dr. H. O. Marsh, *3244 E. Douglas, Wichita 8, Kan.,* Secretary.

Nebraska State Medical Association, Hotel Cornhusker, Lincol April 25-28. Mr. M. C. Smith, 1315 Sharp Building, Lincoln 8, Ne Executive Secretary.

North Dakota State Medical Association, *Dacotah* Hotel, Gra Forks, Apr. 30-May 3. Mr. Lyle A. Limond, Box 1198, Bismarck, N.D Executive Secretary.

(Continued on page 32)

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MALIGNANT TUMORS IN CHILDHOOD

W. B. Kiesewetter, M.D.
and
Edward J. Mason, M.D., Pittsburgh

Malignant disease was diagnosed in 404 of 38,967 children admitted to a hospital during six and one-half years. In children less than one year old, renal and adrenosympathetic tumors were the most frequent type. Thereafter leukemia and lymphoma predominated until the age of 8 years. In the 10-to-13-year age groups, inclusive, tumors of the central nervous system and eye predominated. Twelve cases of bone tumor were observed, all in children past their second birthday. About one-third of the 404 patients came to medical attention because of a mass. The most frequent error at the initial examination was a diagnosis of upper respiratory infection. The two types of malignancy most frequently misdiagnosed were Hodgkin's disease and neuroblastoma. The fact that 75% of those who died from malignant disease were dead at the end of the first 12 months indicates the need for prompt action when the diagnosis is made.

THE importance of malignancy in childhood is growing. Although few articles are published on this subject, the importance of the problem is well reflected by statistics from two other sources. The figure, a modification of a chart put out by the Department of Health, Education, and Welfare Children's Bureau, shows the chief causes of death in persons between 1 and 14 years of age in 1945 and 1955. It is significant that, while there has been a marked decrease in over-all mortality in this decade, there has been an increase in the absolute incidence of malignant neoplasms and congenital malformations. Correspondingly, there has been a relative increase in the importance of malignant neoplasms in the over-all death rate; they now account for 1 in every 8 or 9 deaths in this age group. It is interesting also that malignancy now represents the second most frequent cause of death, having been third in 1945.

Another source of statistical evidence that malignant disease is important in childhood is the fact that in a six-and-one-half-year period ending Dec. 31, 1957, there were 404 cases at the Children's Hospital of Pittsburgh. In the same period there were 38,967 admissions to the hospital, which means that more than 1% of admissions during this period were for malignant disease. The purpose of reporting a statistical analysis of cancer at a children's institution is to examine the problem from the viewpoints both of scope and of success in meeting it. This experience and the follow-up data on these 404 cases are presented in this paper.

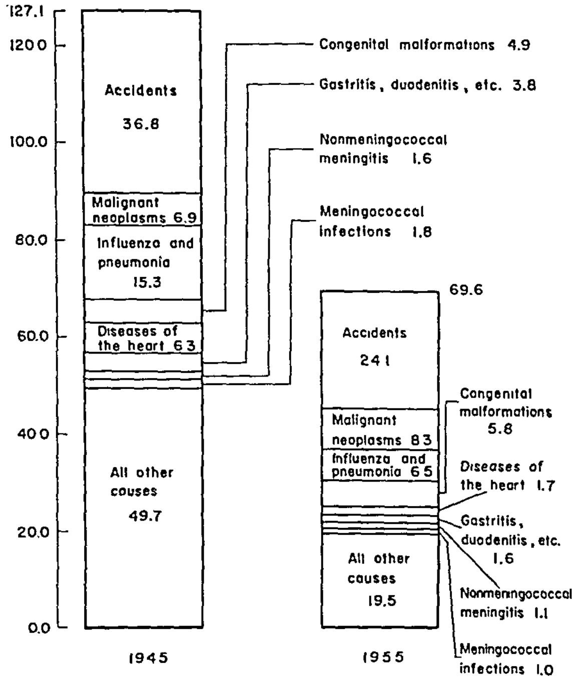
A well-rounded hospital service is offered at this pediatric institution. With the exception of an ophthalmological service, all major medical and surgical subspecialties are represented, and a balanced number of patients are seen and treated by each.

Surgeon-in-Chief, Children's Hospital of Pittsburgh, and Professor of Pediatric Surgery (Dr. Kiesewetter), and Teaching Fellow in Surgery (Dr. Mason), University of Pittsburgh School of Medicine.

Incidence of Cancer

Age and Organ System.—To analyze the material at hand, it is necessary to classify the malignant neoplasms under five general categories, based solely on the anatomic area or organ system, as follows: (1) leukemia and lymphoma; (2) tumors of the kidney, adrenals, and sympathetic nerves; (3) tumors of the central nervous system and eye; (4) bone tumors; and (5) miscellaneous tumors.

In table 1, which portrays the age and organ system incidence of cancer in the total series, several things become apparent. In the over-all aggregate of neoplasms, a child is much more vulnerable to malignant disease under the age of 5 years than thereafter. If one considers those tumors that occur in children from the newborn period through 2 years of age, it is apparent that neuroblastomas and Wilms's tumors predominate in this series. In children from 2 through 5 years of age, leukemia is the principal killer. Above the age of 5 years, while leukemia still takes a large toll, tumors of the central nervous system and eye occur almost equally frequently.



Childhood mortality in United States.

Leukemia and lymphoma are the major killers in this series, accounting for 42% of all cases seen. Second in importance are malignant neoplasms occurring in the so-called flank area, embracing neuroblastomas and Wilms's tumors; these accounted for 21% of the series. In third place were the central nervous system and eye tumors, accounting for an additional 19%. The only other homogeneous group which could be analyzed was that of those occurring in bone; these represented only 3% of the cases. Finally, there was a heterogeneous group of malignancies which could not be broken down into individual groups, and these accounted for the remaining 15%.

Sex and Race.—Negroid and sinoid children appear to be far less vulnerable to malignancy than caucasoid. In spite of the high percentage of negroid children seen as outpatients in the hospital, 391 of the 404 total tumors were in caucasoid children. In this series, there was an approximate three-to-two predominance of males over females, with malignant disease being found in 230 males as against 174 females.

Diagnosis

Attempts to arrive at a diagnosis in the case of these tumors usually center around four different factors. First, if a child had any rapid or chronic changes in growth, this would arouse suspicion of an abnormality, although not necessarily of malignant disease. Such growth changes might be of the entire body or, more commonly, of individual members of the body. Second, any swelling of nontraumatic origin certainly would raise the question of a "tumor." It is usually the "lump" of unexplained origin which does not disappear rapidly that causes a child to be brought under medical surveillance. Third, while changes in temperament, behavior, or intelligence may be due to other causes than a malignant tumor of the brain, these changes occur frequently enough to be a clue not only to this type of malignancy but to malignant processes elsewhere in the body. Such personality changes may occur long before there are manifest signs of the cause underlying alteration of behavior pattern. Finally, more than in the case of adults with tumors, one must be alert to the possibility that any undiagnosed disorder of short or long duration may be caused by an undisclosed malignancy, e. g., leukemia or neuroblastoma.

There are many ways in which total experience with tumors may be approached diagnostically. To make this analysis more comprehensible, patients in this series have been grouped under three headings as they might have appeared to the first physician who encountered the patient. First, the child may have been brought to medical attention because of a mass. Second, a physician might have seen the child because of symptoms directly referable to the mass. Finally, the child might be brought in with nonspecific symptoms which ultimately turned out to be due to malignancy.

Specific Symptoms.—When a mass is the presenting complaint, one thinks of Wilms's tumor or neuroblastoma, in which cases a definite abdominal tumor was palpated either by the mother or by the family physician. Furthermore, the lymphadenopathy which attends leukemia and lymphoma, together with the hepatomegaly or splenomegaly, or both, would be another example of a mass being the initial presenting factor. About one-third (31%) of the total series came to medical attention because of a mass.

An example of the most common symptoms directly referable to the mass in a child would be headache, vomiting, and gait disturbance as the clinical picture of a central nervous system tumor. A child who complained of pain and who limped because of an osteogenic sarcoma would present another example. Of patients in the series, 48% exhibited evidence of the fact that a malignant tumor underlay their symptoms.

Nonspecific Symptoms.—The group of those who had only nonspecific symptoms, which might easily be explained as transitory and of no importance, still constituted one of every five (21%) cases of malignancy. Anorexia, listlessness, weight loss, pallor, and ecchymosis are examples of such symptoms in a child first seeking medical attention.

Diagnostic Errors.—Because of the vague and nonspecific complaints that many of the tumor patients showed, it was not surprising to find a high incidence of wrong initial diagnosis. One hundred fourteen (28%) patients in the total series were not given a diagnosis of malignant disease on admission. To get a perspective on what were the common wrong first diagnoses, these were grouped wherever reasonable. The principal wrong first diagnosis was that of an upper respiratory infection (25%); second in occurrence was rheumatic fever (13%); the third most common error was in patients in whom abnormalities of the spleen were suspected (6%); and erroneous diagnoses of poliomyelitis, meningoencephalitis, and appendicitis each accounted for 4%. The rest of the diagnostic errors were too miscellaneous to permit such grouping. Table 2 shows the type of malignancy connected with the highest incidence of diagnostic error; Hodgkin's disease and neuroblastoma were the most common malignancies in which difficulties in diagnosis led to initial error.

Management

In treating children with malignant disease, one must use certain philosophical principles peculiar to the age group with which one is dealing. Since a child has a lifetime before him, there is little purpose in any type of palliative therapy as the initial approach to his malignant disease. An all-out effort must be made to eradicate the disease process. In our analysis it was found that 298 of 317 patients who died of their disease did so within a two-year period, and the highest proportion of these died in the first year. We therefore must attempt to eliminate the source of malignancy by aggressive therapeutic efforts, even at the price of what seems like a mutilating procedure. It is remarkable how children adapt to the loss of extremities or of the use of certain organs. It is equally true that, in our present state of knowledge, surgery is the main therapeutic agent at our command in the treatment of all of the malignant processes except the leukemia-lymphoma group.

There is an element of urgency in the handling of children with malignancy that is perhaps not as apparent in adults. One never knows which is the day of metastasis as far as a tumor is concerned, and therefore extensive study, with much palpation of a mass, would seem to be detrimental to the child's chances for survival. Therapy should be undertaken as soon as possible after studies have been completed.

A high degree of suspicion must be maintained in the management of undetermined childhood disease, if the wrong first diagnosis is to be eliminated in the case of malignant disease and if these children are to be given maximum therapy at the earliest possible time. Any solid tumor must be considered malignant until histologically proved otherwise. Time and again, application of this familiar adage, when aggressively followed up by biopsy (*in toto* where practicable), has discovered unsuspected malignancies. A child with vague history and multiple symptoms must not be written off as a "behavior problem" but must be watched closely, since these symptoms may be a precursor to out-and-out malignant disease.

TABLE 1.—*Incidence of Cancer in Children by Age and Organ System*

	Age, Yr.															
Disease, Organ or Type	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Leukemia and lymphoma	7	12	22	22	28	22	11	6	9	6	4	2	7	4	8	170
Kidney, adrenals, sympathetic nerves	23	10	12	7	10	4	3	5	2	3	3	1	0	0	1	84
Central nervous system and eye	4	3	6	4	8	8	4	5	3	6	8	1	8	5	2	75
Bone	0	0	1	1	2	1	0	2	0	0	2	1	0	1	1	12
Miscellaneous	14	2	5	9	1	6	2	2	1	2	2	7	3	1	6	63
Total	48	27	46	43	49	41	20	20	15	17	19	12	18	11	18	404

TABLE 2.—*Type of Malignancy Most Frequently Subject to Diagnostic Error*

		Wrong Diagnosis	
Malignancy, Type	Total Cases	No.	%
Leukemia	151	43	28
Hodgkin's disease	19	9	47
Wilms's tumor	33	5	15
Neuroblastoma	51	23	45
Central nervous system tumor	75	16	21
Bone tumor	12	2	16
Miscellaneous	63	16	23
	404	114	28

Results

One does not treat children with cancer long before several facts become apparent. There is a much shorter period of time between the onset of symptoms and the ultimate diagnosis of the child's condition in most cases, compared to malignancies in adults. Perhaps of greater significance is the fact that short-term survival is the rule, if patients are not totally cured of their disease process. This can be readily seen in table 3, which shows the over-all life and death figures in our series. Of the total group of 404, 317 were dead at the time of follow-up survey, an over-all mortality of 80%. Of great importance, and certainly significant, is the fact that 75% of those who died from their malignant disease were dead at the end of the first 12 months. Certainly cancer is an early killer in childhood if it is not completely cured initially.

Table 3.—*Survival Data After Diagnosis of Malignancy*[*]

Diagnosis	Alive				Dead						
	Survival Time, Yr.				Survival Time, Yr.						
	0-2	2-4	4	Total	0-½	½-1	1-2	2-3	3-4	4	Total
Leukemia	1	..	..	1	69	41	29	6	..	3	148
Hodgkin's disease	..	2	..	2	14	2	1	..	..	..	17
Wilms's tumor	3	1	9	13	8	3	7	..	..	..	18
Neuroblastoma	1	4	2	7	21	15	6	2	..	..	44
Bone tumor	3	..	..	3	3	..	5	1	..	..	9
Astrocytoma	..	14	5	19	3	1	2	1	..	..	7
Medulloblastoma	..	1	1	2	6	3	2	2	..	..	13
Other central nervous system tumor	..	4	2	6	17	6	2	..	..	1	26
Thyroid tumor	..	2	4	6	..	..	..	1	..	..	1
Fibrosarcoma	1	2	1	4	..	..	..	..	..	..	0
Miscellaneous	6	5	5	16	20	5	7	2	..	..	34
Total	15	35	29	79	161	76	61	15	..	4	317

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[*] 8 patients were unavailable to follow-up investigation.

Of the 79 patients who survived their malignant disease, 20% were alive less than two years after a cancer diagnosis had been made, while an additional 40% were alive two to four years after diagnosis, and a final 40% were alive longer than four years after malignancy was discovered.

Pathology and Survival.—Table 3 also shows that those childhood tumors which had the best prognosis were Wilms's tumor, astrocytoma, carcinoma of the thyroid, and fibrosarcoma. Admittedly, only Wilms's tumor and the astrocytoma occurred in a sufficient number to permit any statistical inferences. Forty-two per cent of patients with Wilms's tumor were alive at the time of the survey, and the greater proportion of these had survived for more than four years. Among the patients with astrocytoma, a 73% survival rate was written into the record and all of these had survived more than two years. Juvenile cancer of the thyroid was of the papillary type in all seven patients, and six out of the seven survived for more than two years. All four patients with fibrosarcoma also were alive at the time of survey. Since 94% of those who died of their malignancy had died by the end of 24 months, it is interesting that a high percentage of the patients with these four types of tumor not only survived but had passed the critical period of the first two years.

One must look at the other side of the coin to get a true picture of the relationship of the pathology and mortality. All but three of the patients with leukemia and Hodgkin's disease were dead at the time of survey. In addition, two-thirds of the patients with bone tumors had died and the remaining one-third had not had sufficient time elapse to finally evaluate their condition. Only 13% of patients with medulloblastomas and only 19% of those with an assortment of 32 other central nervous system malignancies were alive. Even in those with the heterogeneous group of miscellaneous malignancies, survival was found in only one-third of the cases. Finally, among patients with neuroblastoma, which some writers have believed to carry a better prognosis than other malignancies, there was an 86% mortality in the total group of 51 patients.

Age at Onset.—Table 4 depicts the relation of the age at onset of malignancy to the ultimate mortality figures in the major subgroups of cancer patients studied. The significant fact here is that age at onset seems to play little or no part in the over-all mortality figures, except in the case of the patients with Wilms's tumor and, to a smaller degree, with neuroblastoma. The earlier the onset in these two groups, the better the prognosis; this was particularly true if the age at onset was under 1 year. The rest of the data show little difference between those who developed their disease early and those who developed it later. However, patients with central nervous system tumors seem to have a somewhat better prognosis if they were 4 years of age and older when they had their diagnosis made.

Table 4.—*Relation of Mortality to Age at Onset*[*]

Age at Onset, Yr.	Disease, No.													
	Leukemia		Hodgkin's Disease		Wilms's Tumor		Neuroblastoma		Bone Tumor		Brain Tumor		Miscellaneous	
	A	D	A	D	A	D	A	D	A	D	A	D	A	D
<1	0	7	0	0	5	4	2	11	0	0	1	3	6	5
1	0	12	0	0	3	2	2	3	0	0	0	3	0	2
2	0	22	0	0	3	4	0	5	0	1	0	6	1	4
3	0	21	0	1	0	1	0	6	0	1	2	1	1	4
4	1	25	0	2	0	2	1	6	0	2	4	5	1	1
5	0	20	0	2	0	2	0	2	1	0	4	4	2	4
6	0	8	0	2	0	0	0	3	0	0	2	2	2	0
7	0	5	0	0	0	1	2	2	1	1	1	4	2	2
8	0	5	2	2	0	0	0	2	0	0	2	0	0	1
9	0	6	0	0	2	0	0	1	0	0	2	4	0	2
10	0	2	0	2	0	2	0	1	0	2	2	5	1	3
11	0	1	0	1	0	0	0	1	1	0	0	1	2	5
12	0	5	0	2	0	0	0	0	0	0	2	5	4	0
13	0	2	0	2	0	0	0	0	0	1	3	2	0	1
14	0	7	0	1	0	0	0	1	0	1	1	1	4	3

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[*] A = alive; D = dead.

Follow-up Data

It was gratifying to be able to have follow-up data on 98% of patients in this total series of 404 cases. Follow-up investigation was carried out by reference to hospital charts, by personal knowledge or visit, and by correspondence with families and with other physicians. Among the eight patients whose progress it was not possible to follow, there were three with central nervous system tumors, two with leukemia, two with Wilms's tumor, and one with malignant disease in the miscellaneous group.

Among the 79 patients who were alive at the time of the survey, 5 had evidence of disease. (All ages given are those at time of diagnosis.) One was a 12-year-old boy with carcinoma of the thyroid; he had survived over four years since his original diagnosis and had some evidence of nodulation in the neck. Another carcinoma of the thyroid was in a 7-year-old girl who likewise had survived more than four years since the diagnosis was made; the continuing disease was in the form of roentgenographically visible, asymptomatic lung metastases. A third patient, with a cerebellar astrocytoma, was a 5-year-old boy, and there was local evidence of disease although he had survived over four years since operation. The fourth patient with malignancy still present was a 14-year-old girl who had a mesenchymal mixed tumor of the abdomen diagnosed by biopsy four years previously, with evidence still present of an abdominal mass but no distant metastases. The final patient was a child under one year of age who had a rhabdomyosarcoma of the labia; the patient was unable to have curative surgery performed initially because of the local invasion of the tumor. The recurrence was in the immediate area and extended into the pelvis as an abdominal mass.

Unusual Survivals.—Ten patients in the survival group had unusual histories. Among survivors with central nervous system tumors was one with craniopharyngioma who was alive four years after having his pituitary lesion removed; the only residual difficulty was from diabetes insipidus. In addition, a 10-year-old girl had a medulloblastoma which was treated with excisional surgery and nitrogen mustard; she had been alive for eight years, was married, and, at the time of follow-up, was pregnant for the first time. A pineoblastoma in a 9-year-old girl was apparently successfully removed, for she had survived well over four years but unfortunately was blind.

Among the patients with abdominal neoplasms who have had unusual survivals was an 11-year-old boy with hypernephroma; he had survived over four years. Two patients had histologically demonstrated malignant pheochromocytomas. One was a 12-year-old girl, symptom-free and with no evidence of a lesion four years after surgery, and the other a 6-year-old girl with severe hypertension and what seemed to be an incomplete removal of her malignancy. She was well for two and one-half years with normal blood pressure. One patient with Wilms's tumor, a girl under one year of age at the time of surgery, subsequently had cerebellar metastases which were removed a year after the first operation; her follow-up investigation at the age of 10 years showed her to be completely well.

Three patients with soft tissue malignancies, in which one does not usually expect survival, were of interest. A 5-year-old boy with reticulum cell sarcoma and a 14-year-old boy with giant lymphoblastoma were both living and well two to four years after surgical extirpation. Finally, in a 3-year-old boy with a lymphosarcoma of the nasopharynx excised five years ago, there was no evidence of disease locally or systemically at the time of follow-up investigation.

Summary

A series of 404 children with malignant tumors, seen at the Children's Hospital of Pittsburgh, was analyzed from the standpoints of age incidence, diagnostic leads, management, and results. A six-and-one-half-year survey of malignant disease showed an 80% over-all mortality, with three-quarters of these deaths occurring in the first year after diagnosis.

125 Desota St. (13) (Dr. Kiesewetter).

FEEDING BY INJECTION.—Considered from the standpoint of cellular nutrition, there is little reason to doubt that the needs for various nutrients both in kind and amount are fairly similar whether provided by enteral or parenteral means. The latter differs mainly in that problems concerned with toxicity and availability are accentuated, and in addition the requirements of sterility and non-pyrogenicity are imposed. The fundamental challenge has therefore not been to discover what nutrients are required, but rather how to provide them in suitable forms and amounts. From both experimental or practical standpoints this involves all necessary nutrients, although whether all are employed in practice is a matter of judgment in each particular application.—R. P. Geyer, Parenteral Nutrition, *Physiological Reviews*, January, 1960.

GAS AND OPAQUE CONTRAST IN ROENTGENOGRAPHIC DIAGNOSIS OF PERICARDIAL DISEASE

Herbert M. Stauffer, M.D., Louis A. Soloff, M.D., Jacob Zatuchni, M.D.
and
Barbara L. Carter, M.D., Philadelphia

Differential diagnosis between pericardial disease and other heart conditions has been facilitated by angiography. The hazards of intravenous injections of radio-opaque contrast materials can be avoided by injecting pure carbon dioxide gas. This dissolves rapidly and completely in the blood after serving its purpose. Numerous rapid intravenous injections of 25 to 100 cc. of 100% carbon dioxide have been made in adults without causing subjective discomfort. The apparatus, before the injection, must be flushed thoroughly several times with the gas. The technique of gas angiography described by the authors was used 51 times in 40 patients. With the patient in left lateral position the right atrial border was visualized, which gave positive evidence of disease in 21, normal findings in 18, and equivocal results in 12 cases. In none of the patients studied were there any untoward reactions.

The clinical signs and symptoms, laboratory findings, and roentgenographic changes in pericardial disease are familiar and have been well described. However, the findings from conventional roentgenograms in both pericardial effusion and constrictive pericardial disease are frequently equivocal. Even massive pericardial effusions may at times be difficult to distinguish from cardiac enlargement. Angiocardiography with opaque contrast material has become well recognized in the elucidation of problems in the diagnosis of pericardial disease.[1]

Several years ago one of us, with others,[2] introduced a new method of angiography specifically for studying pericardial disease by outlining the lateral border of the right atrium with intracardiac carbon dioxide gas, which was introduced intravenously. Another group[3] has recently reported favorably on experience with this same technique. This present communication is an evaluation of the relative merits of opaque and gas contrast angiography in the study of problems of pericardial disease in the light of our accumulating experience with the gas contrast method.

Safety of Intracardiac Carbon Dioxide Gas

The studies of Durant and Oppenheimer and their associates[4] established the efficacy of placing the patient with the left side down in the treatment of venous air embolism. In this position, the outflow tract of the right ventricle and the trunk of the pulmonary artery remain dependent and contain blood even though the upper portion of the right ventricle contains gas, so that the blood flow to the lungs and the systemic circulation are maintained. Roentgenograms of dogs' hearts, made during the course of these experimental studies, showed details of intracardiac structures to good advantage. This led to trials of intracardiac carbon dioxide gas injected intravenously for roentgenographic study of the heart. The gas proved to be quite safe for this purpose because of its high coefficient of solubility in blood, which permits it to go rapidly into solution with only fleeting cardiovascular effects. With rapid injection either intravenously or by cardiac catheter the gas remains long enough for roentgenographic visualization of cardiac structure of the right side of the heart.

Studies in dogs[5] showed that large volumes of carbon dioxide gas injected intravenously rapidly (7.5 cc. per kilogram of body weight) produced only a brief decrease in systemic blood pressure, whereas the injection of air causes a prolonged decrease which often causes death. With intravenously injected carbon dioxide there was a brief hypotension and hyperpnea which lasted about 15 seconds. Probably the brief hypotension caused the hyperpnea, since arterial blood and alveolar gases showed only a small deviation from control values. The oxygen level was decreased 0.3 vol. %, and the carbon dioxide level was increased 2.87 vol. %. Alveolar gas levels showed alterations of similar degree. The right ventricular diastolic pressure was increased for 15 seconds when the dog was in the supine position. In all positions the right ventricular systolic pressure was elevated somewhat longer than 15 seconds. The short period of systemic hypotension with high right ventricular systolic pressure resulted from the brief increase in resistance during the time that gaseous carbon dioxide persisted.

Carbon dioxide administered into the left ventricle of dogs by retrograde catheterization produced only slight cardiovascular respiratory changes. The electrocardiogram showed a few extra systoles and an alternans of a few seconds duration. Air injected similarly into the left ventricle killed the dogs to whom it was administered.

From the Departments of Radiology and Medicine, Temple University School of Medicine and Hospital.

Read before the Section on Radiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

The effects of carbon dioxide gas injected intraenously and reaching the left side of the heart hrough an experimentally created atrial septal deect were studied.[6] After such injections gas was emonstrated in both the left atrium and left venricle as well as in the right side of the heart. Under hese circumstances carbon dioxide gas proved to e quite safe for the experimental animals.

Oppenheimer and associates[7] have also recently hown that carbon dioxide gas is well tolerated hen introduced directly into coronary arteries of nesthetized dogs. They used the selective coronary rtery catheterization technique of West, which ermits evaluation of cardiac effects in the absence f systemic action. There were no deaths of patients ith either normal or freshly infarcted hearts. No ersisting changes in the electrocardiogram of lood pressure were produced when the gas was njected slowly over a period of several seconds. apid injections under pressure produced short ns of extra systoles and changes in the T wave hich lasted for a few seconds.

Repeated intracoronary injections of potassium ere used to produce lasting S-T segment deviaon. Intracoronary injections of carbon dioxide gas id not increase, but rather temporarily abolished, e S-T segment deviation.

Numerous rapid carbon dioxide injections have een made intravenously in adults with volumes of 5 to 100 cc. without any subjective discomfort. In o such patients, who received 50 and 60 cc. of rbon dioxide gas, respectively, simultaneous right ntricular pressure determinations by heart cather and electrocardiograms showed no significant teration. These patients were examined in a suine position, and films made with the biplane ngiocardiographic apparatus showed the outflow act of the right ventricle and trunk of the pulonary artery outlined by gas.

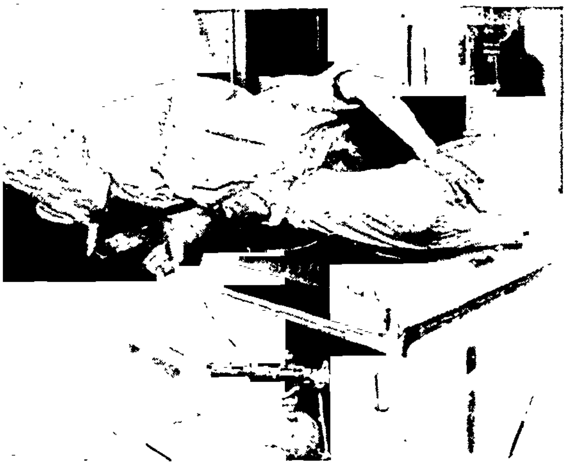

Fig. 1.—Left-side-down position of patient against x-ray ssette changer for intravenous carbon dioxide pericardial udy.

Carbon Dioxide Technique for Pericardial Study

Method.—When the carbon dioxide technique is used for pericardial study, the patient is placed with the left side down and the x-ray beam is horizontal. When the right atrium contains gas its lateral wall appears in the frontal projection as a smoothly curved band, convex laterally, not more than 3 or 4 mm. in thickness under normal circumstances. When pericardial effusion is present a soft tissue shadow appears between that of the right atrial wall and the lung so that a widened band of soft tissue density intervenes between the gas in the atrium and the lung. It has been previously pointed out that this position is the one indicated for the treatment of air embolism. As a further precaution to eliminate any possibility of hazard from a residual bubble, we advocate that the patient be kept in the left-side-down position for 5 to 10 minutes after the last carbon dioxide injection.

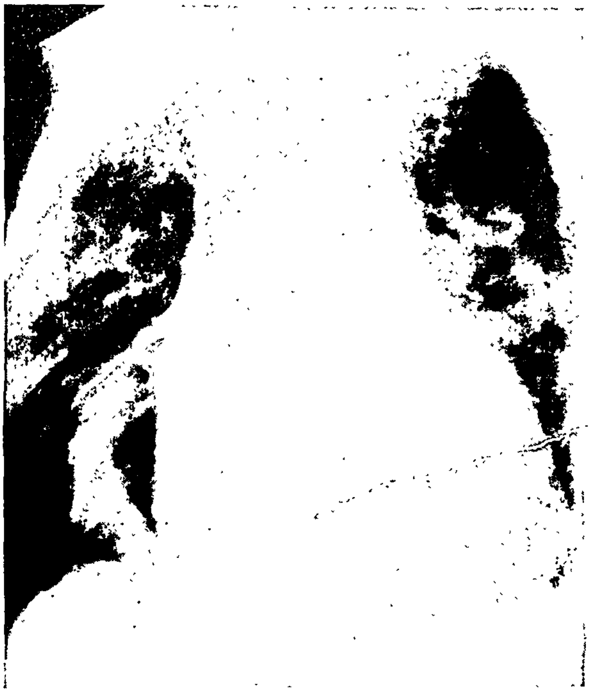

Fig. 2.—Pericardial effusion in heart failure shown by carbon dioxide gas in right atrium.

For the gas angiocardiogram, 100% carbon dioxide has been used. One should be sure that the tank contains pure carbon dioxide and not the usual mixture of carbon dioxide and oxygen available in the hospital. The patient is placed in the left lateral decubitus position, and a 19 or 20 gauge needle is inserted into the median antecubital vein (fig. 1). The needle is connected to an intravenous drip via a three-way stopcock so that the needle can be kept open in the intervals between gas injections. A 100-cc. syringe with another three-way stopcock is thoroughly flushed several times with pure carbon dioxide, and 100 cc. of the gas is then rapidly injected into the vein. An exposure is made at the end of the injection, and a second exposure is made within a few seconds thereafter. The films are checked while wet after processing, and a second injection is made if indicated.

This technique has been adhered to because of our desire to test carbon dioxide visualization in the simplest possible form as a readily available method. The technique of using one or two films, although very simple, has resulted in some difficulties in interpretation which we believe would be obviated by the use of cineradiography or the serial filming technique regularly used with opaque angiocardiography.

Results.—We have done 51 studies of carbon dioxide injection in 40 adult patients with problems of pericardial disease. The volumes injected have varied from 50 to 100 cc. Twenty-one of these studies gave positive evidence of pericardial effusion or pericardial thickening. Eighteen showed negative or normal results with respect to the right atrial border of the heart, and in 12 the findings were regarded as equivocal. In none of the patients studied were there any untoward reactions.

The availability of the carbon dioxide technique has made it possible to undertake a study of the contribution of pericardial effusion to the enlargement of the silhouette in cardiac failure.[8] Nineteen of the patients mentioned above received carbon dioxide injections as part of a preliminary study of this problem. Seven of these patients were demonstrated to have pericardial effusion (fig. 2), in eight the examination showed negative findings, and in four the findings of the carbon dioxide study were equivocal. In the patients with definite evidence of pericardial effusion, review of the original conventional films failed to show distinctive features which would permit the diagnosis of pericardial effusion. It is of interest that reduction in the size of the cardiac silhouette occurred with appropriate treatment for cardiac failure regardless of whether or not pericardial effusion was demonstrated. Also, severe peripheral edema was observed in the absence of pericardial fluid and, conversely, pericardial effusion was noted with only minimal peripheral edema. It is hoped that extension of these studies will provide information of prognostic value.

Scatliff, Kummer, and Janzen[3] have recently reported encouraging results with this carbon dioxide technique in the demonstration of pericardial abnormality. They carried out 19 injections in 16 patients with no serious complications. One patient developed paroxysmal coughing on being turned on his back after the injection of the gas when he was in the left-side-down position. It is not known whether the gas injection was actually directly responsible for this complication.

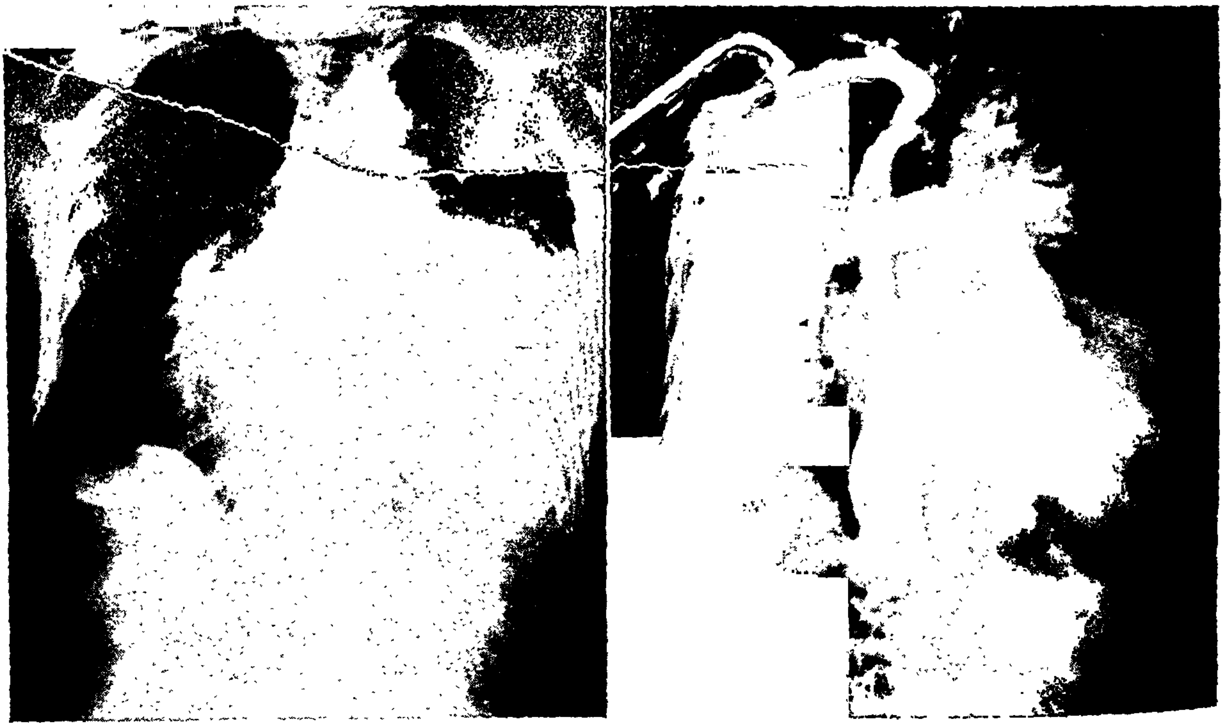

Fig. 3.—Angiocardiogram in massive pericardial effusion.

Relative Merits of Carbon Dioxide and Opaque Angiocardiography

The carbon dioxide technique outlined above for the study of pericardial problems has been demonstrated to be convenient and safe. It may be carried out with the ordinary equipment available in any radiology department. There is minimal trauma to the antecubital vein, since only a small needle need be used. The gas does not irritate the vein. Patients experience no unpleasant sensation with the carbon dioxide injection. On the other hand, opaque contrast material in the high concentrations required for angiocardiography is irritating and may cause vein occlusion; a cutdown is often required for the injection. While improvements in the radio-opaque drugs used for angiocardiography have minimized the hazard due to sensitivity in their use, severe reactions may still occasionally occur. There is no reason to anticipate a sensitivity hazard in connection with the use of carbon dioxide intravenously.

The carbon dioxide contrast technique is particularly valuable in seriously ill patients where a simple nontraumatic and nontoxic method may be vital to demonstrate or exclude pericardial effusion. The treatment is well tolerated even by the acutely ill patient, and it may be used repeatedly to check on the effectiveness of therapy. Although the carbon dioxide method will usually demonstrate the presence of a free pericardial effusion, it does not effectively demonstrate effusions localized elsewhere than over the right atrial border. Similarly, the selective carbon dioxide study permits only a very rough estimate of the size of a free effusion from the thickness of the band of density above the gas in the right atrium. It throws no light on possible cardiac dilatation in association with pericardial effusion. The complete opaque angiocardiogram provides information on these points by showing the relationship between all of the cardiac chambers and the total central mediastinal silhouette (fig. 3).

In constrictive pericarditis there may be characteristic angiocardiographic findings of the kind described by Figley [1a] and by some of us.[1d] These consist of deformity of the right atrial border with loss of the normally smoothly convex contour accompanied by rigidity, which may be demonstrated by the consecutive angiocardiographic films. That such deformity of the right atrial border can be brought out by the carbon dioxide technique is illustrated in figure 4, in which the findings of opaque and gas contrast angiography in the same patient with constrictive pericarditis are compared. The simplified one-or-two-film carbon dioxide technique will not permit recognition of rigidity of the right atrial border. However, such immobility can be demonstrated with carbon dioxide just as with opaque contrast material, provided a serial filming or cineradiographic technique is used. We have encountered one case in which the carbon dioxide study showed a smoothly rounded normal curvature of the right atrial border with some thickening of the wall, which suggested either a small effusion or thickened pericardium. A cineradiographic study was also carried out with carbon dioxide. It showed that the thickened border over the right atrium was quite immobile, which indicated the presence of constrictive pericarditis. This condition was subsequently found on surgical exploration.

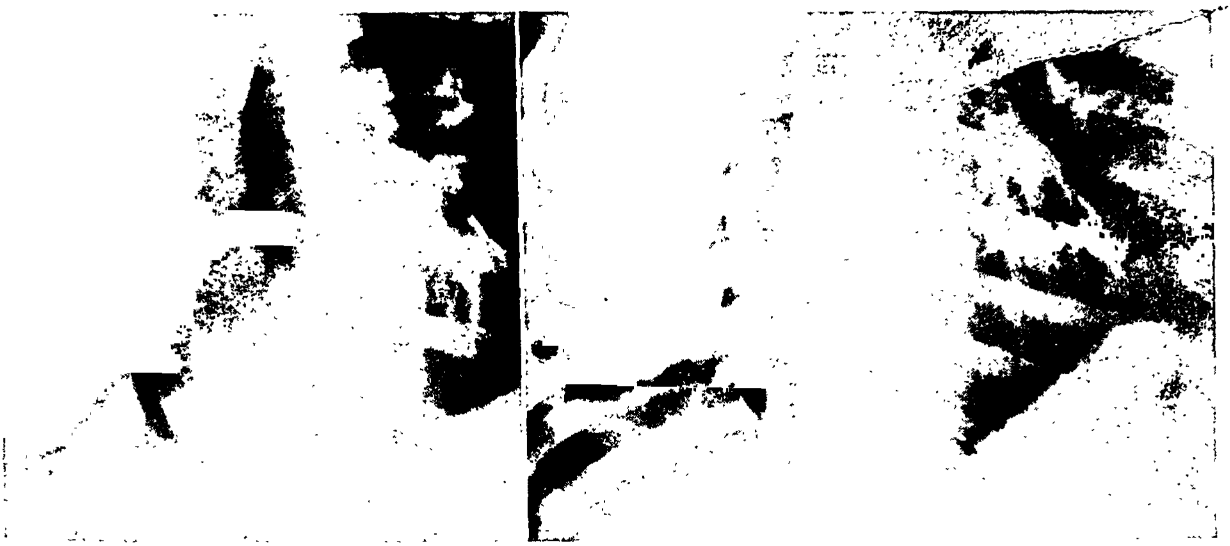

Fig. 4.—Constrictive pericarditis deforming right atrial margin. *Left,* opaque angiocardiogram. *Right,* carbon dioxide study.

Functional information may be obtained by observation of the pattern of flow of intracardiac opaque contrast material in conventional angiocardiography.[9] Thus, the observations of some of us indicate that in pericardial disease prolongation of the intracardiac circulation time is suggestive of underlying myocardial involvement.[1d] Occasional difficulties in interpretation have arisen in using the carbon dioxide technique with one or two films. Extraneous lung markings or pulmonary vessel shadows may sometimes be difficult to distinguish from the right atrial border. An enlarged left atrium may protrude beyond the right heart border and simulate pericardial effusion or thickening of the pericardium. With opaque angiography such overlying structures as the enlarged left atrium and adjacent vessels are outlined with the contrast material and ordinarily do not give rise to confusion. Irregular mixing or streaming of iodide solutions may occasionally occur in the right atrium in opaque angiography and simulate effusion. Evaluation of the pericardial thickness in the presence of pleural effusion, pleural thickening, or extensive abnormal density in the adjacent lung may be difficult or impossible with either gas or opaque angiography.

Conclusions

Intravenous carbon dioxide injection can be safely and conveniently used for roentgenographic demonstration of free pericardial effusion or pericardial thickening localized over the right atrium. Subject to the limitations described, gas contrast study is a useful adjunct to opaque angiography in the study of pericardial disease. It is of particular value in very sick patients or in those needing only a cursory study of the pericardium. Opaque angiocardiography should be done when a more complete study is indicated, particularly for evaluating underlying heart disease. If the findings of gas contrast study prove equivocal, opaque serial angiocardiography may be expected to provide complete morphologic information about the heart chambers, and the flow pattern may provide evidence of underlying myocardial involvement.

3401 N. Broad St. (Dr. Stauffer).

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PENICILLIN IS A POTENT DRUG.—Penicillin causes more deaths than any other drug. Deaths from immediate reactions to penicillin continue to occur. Seven hundred and fifty tons of penicillin are produced and consumed annually. In 1956 Feinberg & Feinberg . . . estimated that more than 1,000 deaths had already occurred from penicillin. Welch and associates . . . in their excellent paper on "Severe Reactions to Antibiotics" surveyed 800 hospitals and interviewed 1,600 physicians, comprising ⅓ of the hospital beds in the United States. They recorded 2,517 reactions to penicillin. Of the total number of reactions 901 were considered life threatening. There were 83 deaths representing a mortality rate of 9 per cent of the latter. None of these 83 deaths had been recorded in the literature. Penicillin was responsible for 84 per cent of the antibiotic reactions. . . . In anaphylaxis, death comes quickly. Aqueous epinephrine (1:1,000) stands alone as the only drug acting quickly enough and effectively enough to prevent it. Our admonition is to give 1.0 cc. subcutaneously at once at the first suspicion of any systemic reaction. This may be repeated as needed.—T. G. Johnston, M.D., and A. G. Cazort, M.D., *Prevention of Deaths from Penicillin*, *Journal of the Arkansas Medical Society,* November, 1959.

ROUTINE CARDIAC FLUOROSCOPY—AN UNNECESSARY HEALTH HAZARD

Eliot Corday, M.D.
and
Henry Jaffe, M.D., Beverly Hills, Calif.

No amount of ionizing radiation, however small, should be considered inconsequential to the patient, to the physician and others engaged in radiologic work, or to their posterity. Young persons especially should be protected against needless exposure. Fluoroscopy involves considerable exposure. This can be reduced by a number of precautions here described. Fluoroscopy should not be allowed to become routine, and when it is necessary it should be preceded by a study of roentgenograms so that the fluoroscopist can concentrate his examination on specific areas and reduce the exposure.

The danger of exposure of patients, physicians and technicians to radiation during diagnostic roentgenographic procedures has become a problem of increasing importance.[1] Thus, the National Committee on Radiation Protection has made the following statement:[1e] "The increasing use of ionizing radiations make it necessary for the medical profession to exercise great caution and restraint in the use of these agents. Current methods in practice should be reviewed to see if the same results could be obtained with less radiation." Swenson[1h] has said: "We must use the lowest radiation output possible remembering that any radiation one gets unnecessarily is too much." He also states[1h] that we must always ask ourselves the question, "Is this examination necessary? Is the need for the procedure greater than the hazard, small though it might be?" Because of the high radiation output during fluoroscopy, many radiologists recommend that this procedure should be used only when absolutely necessary, especially since more accurate results may be obtained by other techniques with a smaller radiation dosage.[1m] Fluoroscopy is one of the most widespread diagnostic procedures used by physicians in the United States. About one-half of all fluoroscopic examinations are conducted by nonradiologists.

The chief reason for the popularity of fluoroscopy is, of course, that it is simpler to carry out than x-ray film procedures. Furthermore, the results are seen immediately; no time need be spent in developing films. The fluoroscopic unit does not require much space and can fit into a small room; the x-ray film unit requires more floor space. In many physicians' offices, space is limited and room for a full x-ray unit is not available. Another reason fluoroscopy is popular in present practice is that expensive x-ray film is not needed for it. Manufacturers have developed compact x-ray units and developing tanks, and many offices now could have these units installed in a limited floor space. Many clinicians continue to use the fluoroscopic unit without proper precautions, knowing full well that they are apt to obtain radiation burns from their fluoroscopic unit (see figure).

I have recently discussed this problem with a renowned diagnostician whose fingers had been badly burned through the use of fluoroscopy. Even though this authority has required skin grafting because of injury to his fingers from radiation, he continues to use fluoroscopy in his routine examinations because he does not have sufficient floor space to install an x-ray film unit. An x-ray film unit would reduce the amount of radiation to which this diagnostician would be exposed.

Danger of Radiation Exposure

The dangers of exposure to ionizing rays are both gonadal and somatic. It has been demonstrated that when gonads are exposed to primary or spray radiation, mutations in the offspring and even temporary sterilization may result. Permanent sterilization of the ovary will occur with a radiation exposure of 300 r and retardation of bone growth in infants with an exposure of 150 r.[11] For this reason, it is necessary that both the x-ray tube and the fluoroscopic screen be well shielded so that exposure of the gonads is minimized. The hazards of a somatic nature resulting from radiation are the possible induction of malignancies such as leukemia, epithelioma, depression of the bone marrow, depilation, ulceration, and dermatitis.

It is difficult to assess what the safe exposure level may be. The National Committee of Radiation Protection[1e] has recently recommended a maximum permissible dosage of radiation to occupational workers and radiologists. It was stated that the average maximum permissible yearly dose should not exceed 5 r. The maximum permissible dose for various age groups has also been estimated. For persons under the age of 18 years who are exposed nonoccupationally to radiation in

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Assistant Clinical Professor of Medicine, University of California at Los Angeles, and Co-chief of the Cardiac Clinic, Cedars of Lebanon Hospital (Dr. Corday), and Professor of Radiology, University of Southern California, and Chief of the Department of Radiation Therapy, Cedars of Lebanon Hospital (Dr. Jaffe).

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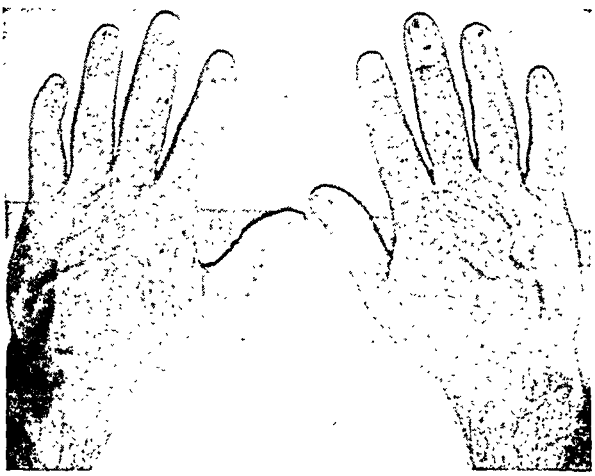
the course of their normal activities but not at their jobs, protective measures should be taken to make sure that they receive no more than 1.5 r. per year. Of course, these dosages were calculated for total body exposure.

It must be realized that during a fluoroscopic examination of the patient, only part of the body is exposed and this would limit the amount of exposure even though spray radiation may occur. Recent investigators have calculated the fluoroscopic radiation dosages the patient receives during a routine examination. Miller [1d] states, "If the duration of the examination is two to five minutes, the dose would ordinarily be 20 to 100 r at the point of entry into the body." For the purpose of comparison, we may mention that the doses given therapeutically for inflammatory conditions, such as furuncles, or thymic conditions are around 50 to 100 r.[11] In other words, the average radiation to which the patient and the fluoroscopist are exposed is in the range of that used in roentgen therapy.



Dorsum of hands of a 52-year-old pediatrician after 25 years of exposure to routine office fluoroscopy. Photograph demonstrates multiple premalignant keratoses as well as atrophy of skin and telangiectasia. Hardening and discoloration of fingernails is also evident.

It has been estimated that taking an anteroposterior and lateral chest x-ray film exposes the patient to as little as 0.002 to 0.005 r.[2] In other words, *the patient will receive about 0.001 of the* fluoroscopic radiation dose during the routine chest x-ray.

In order to reduce the patient's exposure to the minimum, therefore, it would be of advantage to use roentgenography when possible.

Methods of Reducing Radiation Exposure on Fluoroscopy

Because the dosage varies as the time of exposure of the radiation, measures must be taken to reduce the time that the patient is exposed to the radiation. As is well recognized, detail may be more readily seen and the exposure time may be reduced if the fluoroscopist's eyes are accustomed to the dark before the fluoroscopy. For this reason, the fluoroscope should not be used until the fluoroscopist has been in the dark for at least a 15-minute period. Of course, *if the practicing physician has* become accustomed to the dark for 15 minutes prior to each examination, it is obvious that the time allotted to this procedure would cause the cost of fluoroscopy to far exceed the cost of a simple x-ray film.

If he first studied scout films, the fluoroscopist would be aware of the cardiologic or pulmonary problems prior to the fluoroscopy and thus could reduce the time of exposure to the fluoroscope. For instance, if x-ray films demonstrated a mass in the mediastinum prior to fluoroscopy, the investigator could immediately focus on this disturbance and study its movement. The fluoroscopic screen should be shuttered to the minimum aperture. By so doing, the fluoroscopist will receive the minimum amount of exposure. The fluoroscopist must always be clothed in a protective gown and gloves which reduce the amount of exposure.

Comparative Accuracy of Fluoroscopy and Film Examination

Sherman and Cahan [1m] state: "No morphological lesion is revealed fluoroscopically that could not be better shown by film. The basic fault is that fluor*oscopy as a detection or screening* procedure is inaccurate and inferior by comparison with the corresponding film coverage." It has been demonstrated that fluoroscopy can demonstrate only relatively large structural abnormalities whereas roentgenographic examination [3] can reveal smaller ones also. For example, a water density 3 mm. in diameter is often detectable in the lungs by roentgenography whereas a lesion of similar nature must be 5 to 10 times that size before it is regularly visible by conventional fluoroscopy, even under ideal conditions.[3] Many serious lesions readily demonstrable by film examination are impossible to detect fluoroscopically.

One of the most serious disadvantages of the fluoroscopic examination is its impermanence. No record remains except in the memory of the examiner and perhaps in sketches or diagrams which he may make. These cannot compare in accuracy and availability with the permanent record provided by a roentgenogram. Furthermore, several roentgenograms may be compared side by side at any time.

Fluoroscopy has the further disadvantage that it must be done hurriedly in order to minimize the time of exposure of both patient and physician. Roentgenograms, on the contrary, may be examined and studied carefully and deliberately. In addition, they are always available for the opinion of a colleague or consultant.

Sherman and Cahan [1m] state: "When it is indicated, fluoroscopy can be kept to an absolute minimum only when it is integrated with or follows filming. A directed fluoroscopic study based on prior films permits smaller fields and more rapid judgement. When the same information can be obtained by film, fluoroscopy should never be used."

Indications for Fluoroscopy of the Chest

Knowing that the patient and the fluoroscopist should be exposed to as little radiation as possible, we must reexamine the indications for cardiac fluoroscopy and ask ourselves if there are other ways of obtaining the same information with less radiation. Many radiologists[4] have recommended that the routine or isolated cardiac fluoroscopy be abandoned and that this procedure be used only if the posteroanterior and lateral roentgenograms reveal some cardiac abnormality that requires further investigation. Many[5] have stated that posteroanterior and lateral roentgenograms of the chest will reveal most of the cardiac abnormalities that may be found on fluoroscopy. The radiation to which the patient is exposed is 0.001 of that to which he is exposed during routine fluoroscopic examination. On the other hand, many cardiologists believe that by studying the motion of the heart they have a better understanding of the patient's problem. Their reasons for this belief are difficult to express, which makes one wonder if they are valid.

Actually, there is little to be observed from the motion of the heart that cannot be observed from the routinely taken roentgenogram, except paradoxical pulsations due to ventricular aneurysms, the hilar dance, and movement of the diaphragm. However, the accuracy of the interpretation of the movements of the heart depends on the ability of the fluoroscopist, and more accurate information may be obtained by either the roentgenkymogram, which is a graphic photograph of the degree and direction of movement of the heart, or with the new cinefluorographic technique. Aneurysm of the ventricles can also be suggested by abnormalities shown in an electrocardiogram. Rigler[1n] has made the following statement.

> Fluoroscopy is of value in determining the amplitude of pulsation of the pulmonary artery and its major branches; however, the conventional chest x-ray or Roentgenogram will usually reveal such enlargement of these structures as to indicate clearly that a shunt is present. In a differential diagnosis of post-stenotic dilatation of the pulmonary artery and primary pulmonary hypertension, it may also be of some importance. Fluoroscopic examination for aneurysm of the aorta requires a great deal of radiation exposure because movements of the mediastinum are difficult to visualize. The Roentgen-kymogram will also demonstrate aneurysm of the aorta with much less exposure and more certainty.

A search for calcification of the valves may indicate a need for fluoroscopy, but the calcification can also be demonstrated by special x-ray techniques which require far less exposure to radiation. Fluoroscopic visualization of the barium swallow is often used to demonstrate encroachment on the esophagus by an enlarged left atrium. This information may also be obtained with the barium swallow with the right anterior oblique roentgenogram. Chamber enlargement may be discovered from routine posteroanterior, lateral, and oblique chest films as efficiently as with cardiac fluoroscopy. Electrocardiograms may demonstrate chamber enlargements more accurately than radiologic methods.

The fluoroscope vividly reveals paradoxical movement of the diaphragm, but paralysis of the diaphragm can also be demonstrated by chest films made during maximum inspiration. In summary, there is little information obtainable from fluoroscopy of the chest that cannot be learned from routinely made films of the chest with greater accuracy and much less exposure to radiation.

Cinefluorography

This new technique, which has now been made practical, exposes the patient to far less radiation because of intensifier screens. It records the image with a motion picture camera.[6] Thus, the physician using this technique has the advantage of having permanent records that may be studied time and again without repeatedly exposing the patient to radiation. The image, when projected on the motion picture screen, is many times larger than that seen on the fluoroscopic screen, so that details of the movements of the heart and other structures may be more accurately determined. Cardiac catheterization teams are exposed to large amounts of radiation, and most of the members of the teams studied in our survey that are working with the fluoroscope have developed signs of excessive exposure, such as depilation and splitting of finger nails. The use of the intensifier screen and cinefluorography is definitely indicated for this group of dedicated workers.

Summary and Conclusions

Every physician ordering or using ionizing radiation has the moral responsibility of keeping the exposure of patients to a minimum. Warren has recommended, "If each physician would ask himself before ordering the diagnostic procedure 'Is this really necessary' much unnecessary radiation could be avoided."[11] Many patients believe that the examination is not complete unless the fluoroscope has been used. In some instances, fluoroscopy has been used during each visit of the patient. The clinician must realize that this practice is improper and should be curbed. The patient's demands should not dictate the type of examination. The old axiom that every patient presenting himself to a physician, regardless of his condition, ideally should have a fluoroscopic examination of the chest is now outmoded.

Where possible, roentgenograms of the chest should be routinely used prior to cardiac fluoroscopy and the fluoroscopic examination should be used only when there is a definite indication that cardiac or pulmonary abnormalities require further study. "No amount of radiation, however minute, can be considered entirely inconsequential to the individual and the race."[1m] For this reason, fluoroscopic screens must be used at a minimum aperture, the unit should be checked to be sure that it does not overexpose the patient to radiation, the fluoroscopist must always accustom his eyes to the dark so that the exposure time is minimized, and roentgenograms of the chest should always be made prior to the fluoroscopy so that the fluoroscopist may concentrate his examination on specific areas. Because of the increased danger of gonadal changes in children, radiation of younger persons should be very limited.

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PATHOGENESIS OF CORONARY ARTERY DISEASE

M. Jay Flipse, M.D., Miami, Fla.

Many aspects of the pathogenesis of coronary artery disease remain to be clarified, and particular interest centers on the metabolism of fats. The author has studied the reactions of patients to different diets by standard chemical studies of total lipids, phospholipids, and cholesterol in the blood and also by a study of the particle-size of the liproproteins of the blood. The results led to the conviction that the diet of patients with coronary artery disease should be designed to maintain the total blood lipid levels as well as the various fractions within normal limits. This is accomplished by limiting the daily intake of total fat to 50 Gm. and keeping the intake of saturated fats as low as possible.

It is my purpose to outline briefly several modern concepts connected with the pathogenesis of coronary artery disease. Because the literature on the subject is so abundant, I will mention only a few of the authors who are helping to formulate present concepts. The bibliography will accordingly be deficient.

The importance of the subject of coronary artery disease is readily appreciated not only by physicians but also by intelligent laymen. Much has appeared in lay writing about heart disease and its relation to cholesterol levels and obesity. It has been repeatedly emphasized in the press and on the radio that diseases of the heart and blood vessels are responsible for more than half of all deaths and that a large precentage of such diseases develop from coronary artery disease. We must therefore take a stand on diet and medication, not only

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Chairman's address, read before the *Section on Diseases of the Chest* at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

for the treatment but also for the prevention of atherosclerosis. During the last decade considerable progress has been made in explaining at least some of the mechanisms of the development of coronary artery disease. It has long been noted that the process of atherosclerosis is begun by the depositing of fat droplets and cholesterol crystals in subintimal plaques and that the plaques follow a specific pattern of evolution which after slow progression ends either with a rupture of the plaque with discharge of the semifluid contents into the lumen of the artery or with the forming of a thrombus at the site of the plaque, which may later cause an occlusion of the artery. However, the exact explanation of the mechanism is still not available. It is presumed that there is first some defect in the arterial wall which marks the location of a future plaque. It has been noted that there is an increase in the vasa vasorum beneath the plaque. Is the increased blood supply to the media at that site the cause or result of the plaque?

Texon[1] has recently advanced an attractive hypothesis to account for this primary location. With use of Bernoulli's theorem pertaining to the lifting effect of fluids passing over a curved surface, he explains by hydrodynamics not only the selection of the site but also the mechanism of the rupture of the plaque when distended with semifluid contents. The fact that forces sufficient to produce these effects are present in the coronary arteries can be accepted in view of the parallel fact that the upper side of the convex surface of an airplane wing exerts sufficient lift to keep the plane aloft in flight. Inquiry into the process of atherosclerosis has also been directed toward the study of experimental atherosclerosis in animals and an attempt to determine some common denominator to explain the process in man.

Heredity, Age, and Sex

It was inevitable that statistical studies would bring out the importance of factors such as heredity and the tendency for atherosclerosis to run in certain families.[2] Many early observers noted the association of atherosclerosis with diabetes and hypertension. Longevity, it was implied, depended on the condition of one's arteries. In words ascribed to our great teacher of medicine, Sir William Osler, "A man is as old as his arteries."

Additional study indicated that there were possibly some racial factors of importance. In Oriental persons, it was noted, atherosclerosis and hypertension were uncommon. However, it was subsequently observed that when Oriental persons were transplanted to families in the United States and lived on their diets, they developed hypertension and atherosclerosis almost as readily as Caucasians. It turned out that what appeared to be a racial immunity perhaps was only related to dietary habits. Additional studies[3] of the ethnic groups of South Africa[4] have likewise indicated the importance of the fat in the diet as a concomitant mechanism associated with the incidence of atherosclerosis and its complications. Sex is also an important factor. Coronary thrombosis is 24 times commoner in men than in women under the age of 40 years. For people in the 40's the ratio is 5:1, 2:1 for those in the 50's, and 1:1 for those over 60.[5] Not as many women as men die of atherosclerosis, either of the coronaries or of other arteries, because they usually do not get it until they are older.

Studies with hormones in experimental laboratories have indicated that estrogenic substances act as a protective mechanism. Robinson and coworkers[6] reported that the lipid pattern of women past the menopause is distinctly different from that of young women and indicated that the post-menopausal pattern may be reversed to the more youthful pattern by the administration of estrogenic hormones. These authors believe that the difference in the lipid pattern is perhaps responsible for the increasing incidence of coronary artery disease in older women.

The relation between the incidence of coronary artery disease and age is well known.[7] The rate of deaths from arteriosclerotic and coronary heart disease is only 10 out of 100,000 males 25 to 37 years old but increases to 88 of those 37 to 45 years old, to 365 of those between 45 and 54 years old, to 870 of those between 55 and 64 years old, and to 1,719 of those between 65 and 74 years old. The index is only 2 in 100,000 for women 25 to 34 years old; 14, 76, and 305 for women in the next three age groups, and 947 for those between the ages of 65 and 74. It is evident then that the index increases with age in both sexes but reaches a maximum earlier in men than in women.

Psychic Stress and Effort

Psychic stress as a factor contributing to coronary disease is the subject of considerable controversy. Dunbar,[8] Arlow,[9] and Menninger[10] think that people with a certain specific personality pattern are predisposed to coronary disease. Others,[11] however, do not agree with this theory. If psychic stress were a prominent factor in coronary disease or acute coronary deaths, Hitler would not have required the gas chamber to eliminate 6 million Jews in his attempt at genocide.

There are factors of increased epinephrine production, increase in clotting tendency, and other mechanisms which have been cited by Wasserman[12] as mechanisms that could contribute to postoperative clotting tendencies. Similar claims have been made by Selye,[13] who cites such factors as contributing to organic changes in the blood vessels and thereby predisposing the blood to intravascular clotting. There is no doubt that coronary pain of true anginal type does develop with both physical and psychic stress. It is, however, less probable that the mechanism is significant in the over-all picture of coronary disease, either in the production of the vascular disease or in the final attack of thrombosis.

Master[14] in a large series of cases showed that coronary thrombosis occurred equally often among people of all trades and professions as well as at all hours of the day and night. His studies indicated that each profession furnished its proportionate share which was numerically similar to the percentage of the population engaged in the specific profession or trade. He also indicated in his studies that the time of the onset of the attack bore no relation to physical activity.

Physical strain or effort is often cited as a cause of acute myocardial infarction. No doubt acute coronary insufficiency occasionally results from a severe and prolonged effort, but this appears to be a rare occurrence. It has been shown that the average man engaged in his regular employment works much less strenuously than he does when employed in pleasurable activities or sports.[15] Plotz[16] believes that workers in strenuous occupations sustain fewer attacks than sedentary workers.

Diet

It would appear that diet is perhaps the most generally accepted and still the most controversial of all etiological factors pertaining to atherosclerosis. The public has already been introduced to the idea of the importance of cholesterol. Whether cholesterol levels per se are directly associated with atherosclerosis has not been established however. The importance of the phospholipid fraction of blood fats has likewise received attention. There is good experimental evidence that the ratio between cholesterol and phospholipid may be of considerable importance in the development of experimental atherosclerosis in laboratory animals.

While, in general, the fats in the diet are held responsible for the vascular changes of atherosclerosis, there is no present agreement about what part the lipid intake or synthesis contributes to the primary source of the trouble. The cholesterol-poor diets of yesterday have been superseded by the low-fat diets or low-saturated-fat diets of today.

The importance of starvation in the reduction of hypertension was well demonstrated by the people of Europe during the last world war. Selye[13] says, "During the second world war, among the undernourished populations of Belgium, Soviet Russia, and German cencentration camps, there was a definite tendency toward hypotension and bradycardia, while the incidence of hypertensive disease was extraordinarily low." Among the obese, starvation or partial starvation in fats and carbohydrates is certainly capable of drastically reducing the total amount of blood fats. Thus the diet of Kempner, in which the fat and sodium were markedly restricted, not only controlled hypertension but also caused a reversal of the atherosclerotic changes in the retinal vessels.[17] This astounding demonstration of the reversibility of the process of atherosclerosis has warranted the hope that some program may be devised which will not only prevent an extension of the disease but also cause a reversal of at least part of the damage that has already been done.

There is another school of thought which is ably supported by Gofman,[18] who has made extensive studies on the size of the fat particles as they appear in the blood plasma. He has identified two classes of lipoproteins as being particularly significant in atherosclerosis. These lipoproteins, which are of a size identified as S_f 0-12 and S_f 12-400, show uniformly increased levels in persons who have sustained myocardial infarction or have symptoms of atherosclerosis. In a series of monographs and other publications, Gofman has expounded his beliefs and pointed out the group of lipoproteins influenced by an increased fat intake and also the group of lipoproteins influenced by an increased carbohydrate intake. In his recent book for the laity, "Dietary Prevention and Treatment of Heart Disease," he has recommended certain diets. A review of these diets will show that they are of ketogenic character but that the fats are derived from unsaturated instead of saturated fats. It would appear that, of all the investigators, Gofman and his associates are at the present time more completely convinced of their own position than are the exponents of any other schools of thought and are ready to gamble on the accuracy of their observations by recommending a complete change in the dietary habits of the nation. Confirmation of the prognostic value of Gofman's atherogenic index has recently been reported by Schlessinger.[19] Others,[20] however, believe that the cholesterol values are as useful as Gofman's index.

I have studied a number of patients not only with Gofman's method but also with the standard chemical studies of total lipid, phospholipid, and cholesterol levels and have observed the reactions to different diets. In most instances the high unsaturated fat intake in Gofman's diets resulted in an increase in total lipid levels, although at times it did reduce the cholesterol level and shift the cholesterol-phospholipid ratio to normal limits. I prefer to maintain all factors, including total lipid levels, as near to normal as possible, and therefore in diets which I prescribe at present I reduce the total fat volume to a modest 50 Gm. daily with as low a saturated-fat intake as possible. The results of this regimen, while not perfect, give me better values for the lipid levels than do other diets.

Most authorities advise cessation of the use of tobacco, particularly cigarettes, in persons with *manifest coronary disease. With this* advice I completely agree. The question of alcohol is more controversial. It appears to me that the decisive factor here is the question of the blood fats. When the lipid levels are high, alcohol adds more calories that behave like fat calories in the diet. I usually, therefore, withhold alcohol from those who have manifest coronary disease and also from others who because of their elevated blood lipid levels are candidates for atherosclerosis. Any resemblance of alcohol to a relaxing drug is purely coincidental. For this purpose a tranquilizer is much more effective and less detrimental.

In spite of the multiplicity of observations and the increasing knowledge pertaining to atherosclerosis, there is as yet no single mechanism which can be generally accepted as the primary etiological factor producing this disease. That the problem will be solved in the future cannot be denied. It is, however, necessary to tell our patients something at this time rather than to defer our advice until some future date.

Summary

On the basis of our present knowledge the following facts can be accepted and applied. 1. Excessive body weight contributes to atherosclerosis and shortens life expectancy, particularly in males. 2. Eating excessive fat is not conducive to longevity. 3. Physical activity within capacity is helpful and beneficial in the maintenance of health, probably because of the effects of increased metabolism on carbohydrates and fats. 4. The sex differences in atherosclerosis have something to do with sex hormones. 5. Diabetes and hypertension speed up the process of atherosclerosis and increase the frequency of coronary and cerebrovascular accidents.

The final word on atherosclerosis has not yet been written. Until the problem is completely solved, the medical profession must have an open mind and await new discoveries. Meanwhile, our present knowledge is sufficient justification for careful control of dietary fats.

550 Brickell Ave. (32).

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THE CARPAL TUNNEL SYNDROME.—Anything that narrows the carpal tunnel can and does compress the median nerve, and if abnormal pressure is allowed to continue, irreparable damage to the nerve and its function will occur. The snydrome of median-nerve compression in the carpal tunnel consists of painful paresthesias involving to varying degrees the thumb and first two or three fingers of one or both hands, or weakness and disability of the thumb, or both of these sensory and motor phenomena. . . . The diagnosis of the carpal tunnel syndrome is usually quite easily made if the diagnostician is aware of the condition and has reason to suspect its presence. . . . The onset usually is insidious and symptoms may be present for a long time before the patient consults a physician. On examination often the appearance of the hand, or both hands if the lesion is bilateral, is sufficient to justify a presumptive diagnosis. If the thenar muscles are wasted the depression in the thenar eminences will be obvious and pathognomonic of median-nerve disturbance. The absence of motor disturbance above the wrist will indicate the wrist as the site of the lesion.—J. G. Love, M.D., Median Neuritis due to Pressure in the Carpal Tunnel, *Medical Record and Annals,* July, 1959.

CONTROLLED TRIAL OF METHOXSALEN IN SOLAR DERMATITIS OF CHIPPEWA INDIANS

Robert R. Schenck, M.D., Redlake, Minn.

A markedly seasonal dermatitis, characterized by erythema, edema, vesiculation, and crusting, occurs among American Indians. The possibility of preventing it by administration of methoxsalen was studied in 13 members of a group of Chippewa Indians living in Minnesota. The course of the dermatitis during two-week periods of medication with methoxsalen was compared with its course during periods of placebo administration. The results showed that regardless of medication most patients improved under limited controlled exposure to sunlight whereas in outpatients methoxsalen, in a dosage of two 10-mg. capsules per day by mouth, caused a worsening of the condition in six of the nine patients evaluated. Lactose produced a variety of responses in 10 patients. Since the most important etiological factor in the dermatitis was exposure to sunlight, the wearing of wide-brimmed hats and other protective covering was advised as the logical method of prevention and treatment.

One of the challenging clinical problems seen among the Chippewa Indians in Minnesota is dermatitis actinica. Usually exposed areas, such as the cheeks, nose, lower lip, ears, dorsal surfaces of the hands, and the V-area of the neck are involved, the condition arising in the spring and lasting throughout the summer. Onset of cold weather, with less solar radiant energy per day and the tendency to spend more time indoors, is associated with improvement. The lesion constitutes an overreaction to sunlight, with erythema, edema, vesiculation, and crusting. Secondary infection, especially in the areas around the nose and the mouth is the rule. Many afflicted persons develop a chronic and severe impetigo, with brawny induration or atrophic scarring of the affected areas. It tends to recur year after year in the same persons. The presence of sensitivity to sunlight in persons with a moderate degree of pigmentation is a most fascinating phenomenon.

The properties of methoxsalen suggested that it might be of value in increasing skin tolerance to solar radiation in these patients. The report of Becker [1] clearly showed that the use of the drug combined with carefully measured exposure to ultraviolet rays promoted two epidermal changes of a protective nature. First, the stratum corneum became thickened and more dense than control areas, with formation of a stratum lucidum. Secondly, because of increased adherence of the cells of the epidermis, melanin pigmentation was more efficiently retained. These changes markedly increased the minimal erythema-producing dose of midultraviolet rays, and even six months later it required twice as much energy to induce erythema in the treated areas than was the case in the control sites. Further, Imbrie and co-workers [2] confirmed and extended Becker's report, by showing that persistent tolerance for sunlight which lasted for weeks would result from a single orally given dose of methoxsalen combined with solar exposure. In a well-controlled study Stegmaier [3] reported that a 20-mg. dosage regimen of methoxsalen compared to placebo caused increased tanning (98% confidence level) and decreased burning of the skin (90% confidence level). The *Medical Letter* [4] reported, "A trial of methoxsalen is warranted with albinos or light-complexioned persons who require protection from the harmful effects of sun rays because of occupation or habits." Although the Chippewa Indians appear to be of medium or dark complexion, it seemed to me that those with solar dermatitis were reacting more like light-complexioned persons. The final definition of why this should be so invites further study of the anatomic structure of the skin, comparing the skin of Indians (with and without dermatitis actinica) to that of similar groups of non-Indians.

Potential systemic toxicity was not a serious concern, for Sulzberger and Lerner [5] have pointed out that "the original fear that methoxsalen might cause liver damage has not been proved in a single case." Even more reassuring was the fact that psoralens are widely distributed in foodstuffs—for example, in parsley, celery, parsnips, huckleberry, cloves, figs, and some citrus fruits.[6]

Materials and Method

The Indian Hospital at Redlake provides medical and dispensary care for nearly 3,000 Chippewa Indians. During the summer months I regularly saw 20 or more patients with dermatitis actinica. During the months of July and August I studied 13 patients. Of these, 11 were induced to enter the hospital for initiation of treatment for one-week periods. This enabled controlled exposure to sun-

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Formerly Clinical Director, U. S. Public Health Service, Indian Hospital. Dr. Schenck is now a student at the School of Tropical Medicine and Hygiene, London.

light. Two were treated exclusively as outpatients. The group ranged in age from 9 to 61 years and four of the patients were male.

Alternate patients were given two capsules of a medicament daily, two hours prior to solar exposures according to the schedule presented in table 1. The capsules, which were supplied under a numerical code, contained either methoxsalen, 10 mg., or were placebos (lactose) of identical appearance. Pretreatment 35-mm. color transparency photographs were taken of all subjects. Other photographs were taken at weekly intervals during and after the periods of drug administration, so that most patients had five photographs taken over a four-week period. In addition, "follow-up" photographs were taken of some patients.

Table 1.—*Schedule of Solar Exposure of Patients with Dermatitis Actinica Treated with Coded Medicament*

Treatment	
Methoxsalen or Placebo, Day of Treatment	Length of Exposure to Sunlight in Minutes
1	5
2	8
3	11
4	14
5	17
6	20
7	25
8	30
9	45
10	60
11	75
12	90
13	120
14	180

At the beginning of the study, patients alternately received one of the two coded capsules for an initial two weeks of administration. During a second two-week period the remaining coded capsule was given. Thus each patient who completed participation in the study received a total of four weeks of treatment. The first and third week was spent in the hospital by 11 of the 13 subjects. During these periods the exposure to sunlight was accurately timed with watches by the nurses. Careful explanation and instruction was given to all patients for proper exposure while at home, for 2 were treated as outpatients while the remaining 11 were discharged during the second and fourth weeks of the study.

Results

Of the 13 patients, 7 received the placebo and 6 methoxsalen during the initial two weeks of treatment. During the third and fourth weeks, when the medication was switched, a few subjects would not continue participation in the study. Thus, only five received the placebo and three methoxsalen during the second course of medication. This enabled a total of 19 evaluations of two-week periods of treatment to be made. In addition, evaluations and photographs were made of the inpatients on their discharge from the hospital after one week of treatment. Altogether there were 12 trials with the placebo and 9 with methoxsalen, enabling 36 separate evaluations to be made at weekly intervals. Six scheduled evaluations were not done because of the patients' failure to return, at the end of one week in four instances and at the end of two weeks in two.

Three independent observers reviewed the serial kodachrome transparencies, and the findings of each were fairly consistent when compared. These results are found in table 2. It became apparent that 9 of 17 patients showed improvement after one week of hospitalization. However, seven of these had received the placebo. It was believed that the relative lack of exposure to sunlight while in the hospital under control conditions was responsible for this improvement.

After a week at home, the patients treated with placebo showed a variety of responses; the condition of two became worse while that of four improved. The condition of patients who received methoxsalen during the week at home became worse in six and remained unchanged in three instances; in none of the patients was there improvement with methoxsalen therapy during this period. Of the six patients whose condition deteriorated, several had manifestations or exacerbations of complicating impetigo.

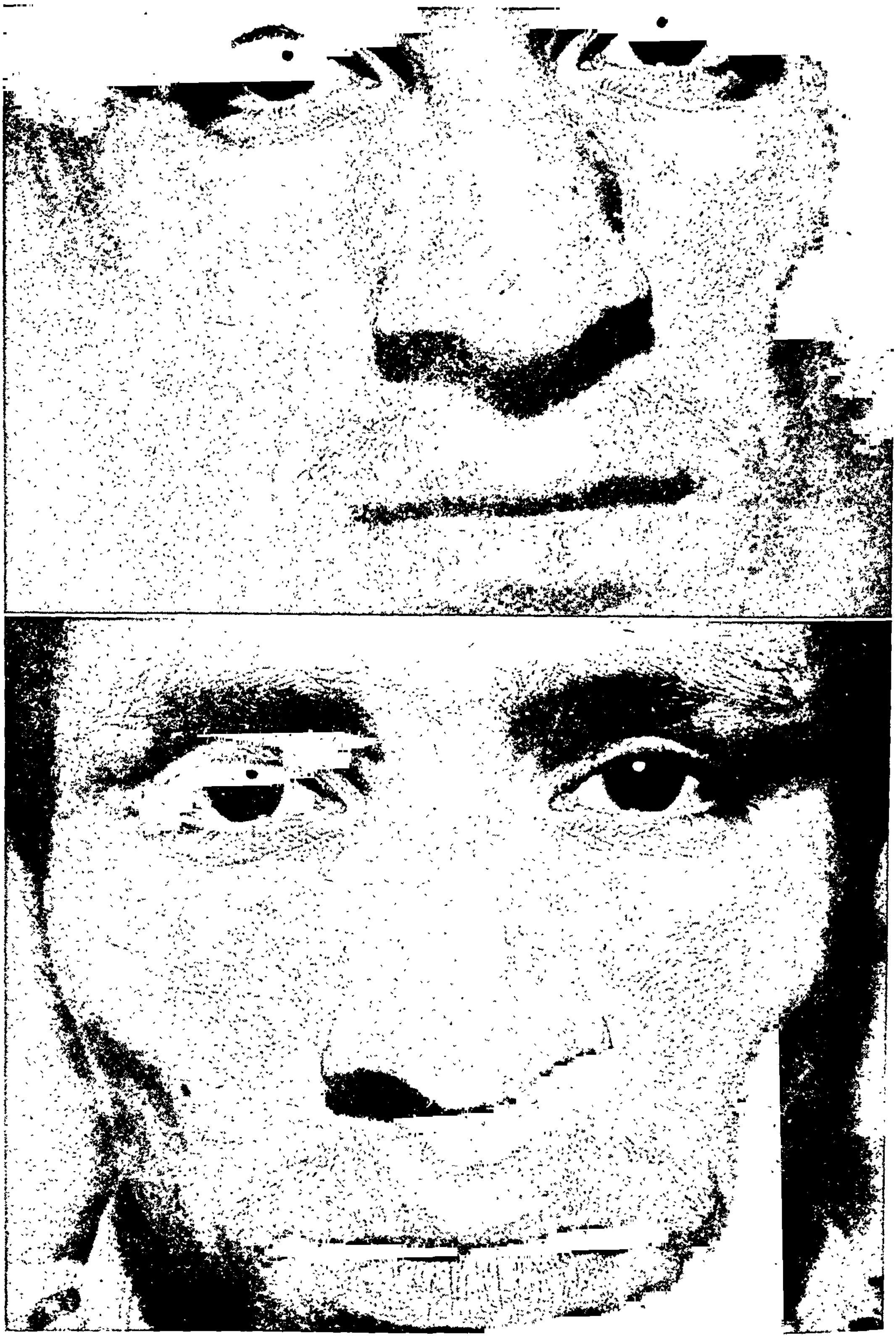
Comment

The presence of solar sensitivity in Indians at first seemed unlikely because of the relatively dark color of exposed areas of skin. The natural course of the process, however, showed that exacerbation or improvement depended on exposure to the sun or protection from it. Exposure was, in general, excessive, because the typical small house is used primarily at times of eating and sleeping during the summer months. Protective clothing, such as wide-brimmed hats, was seldom worn. Further, most employment involved outdoor jobs. An earlier suggestion that dietary deficiencies might be involved is untenable, because the Chippewa Indians' diet is best in the summer, when such garden products as vegetables and blueberries are present. In the winter, when their diet is poorest, the dermatitis spontaneously clears. If indoor employment was obtained in the summer the condition was likewise found to improve.

Table 2.—*Results of Comparative Trial of Methoxsalen and Placebo Combined with Solar Exposure in Dermatitis Actinica*

	Therapy			
	Placebo		Methoxsalen	
Clinical Condition	End 1st Wk.	End 2nd Wk.	End 1st Wk.	End 2nd Wk.
Worse	0	2	2	6
Unchanged	1	4	5	3
Improved	7	4	2	0

It is important that this situation become better known, for once the etiological role of sunlight is recognized, steps may be taken to minimize ex-



Patient treated for dermatitis actinica. *Top,* lesion covering bridge of nose and cheeks prior to hospital admission. *Bottom,* one week after administration of medicament (either methoxsalen or placebo) and solar exposure there is marked improvement in condition. When code was broken, it was found that patient had been given lactose placebo instead of methoxsalen.

posure. Although the entity is being diagnosed by a few dermatologists who treat Indians, many other practitioners have not considered the true etiology. It is also important not to confuse this entity with other, more serious, conditions. The patient shown in the figure, for example, had undergone extensive studies to rule out acute lupus erythematosus because of the butterfly distribution of his facial lesions.

As to the role of methoxsalen in preventing or ameliorating the condition, it seemed likely that carefully timed exposure to sunlight in early spring might induce the protective changes described by Becker. This could be of distinct help to those not already sensitized, although it may be possible that the skin has been irreversibly made prone to the lesion in those who have developed the syndrome.

This study would indicate that the use of methoxsalen in patients in whom the syndrome is already developed and presently active serves no useful purpose and is probably contraindicated. The increase in severity of the condition during the second week of therapy in six of the patients reported by me might in some ways be explained by the findings of Becker[7] that combined therapy with methoxsalen and ultraviolet light produced greater inflammation than the control medicament. This was manifested by a greater amount of infiltration about the superficial vessels of the dermis, as disclosed by biopsy specimens taken on the 14th day of short-term administration of methoxysalen. Undoubtedly another factor played a role in the adverse response to methoxsalen while patients were at home. For, despite the careful directions on the length of exposure to ultraviolet light, it is likely that the specified exposure of 30 minutes per day on the day of discharge (8th day of treatment) to 3 hours on the fourteenth day was not strictly observed. This can be explained by the mode of living of Chippewa Indians, and the usual lack in their homes of conveniences such as plumbing and indoor lavatories. In this respect the outpatient phase of treatment simulated more closely the usual field conditions met in medical practice.

It is possible that, if methoxsalen is given in early spring, prior to the activation of the dermatitis, the condition may be prevented or ameliorated. Because of the excessive solar exposure inherent in the Chippewa Indian's way of life, however, a more practical preventive might be to encourage or even to insist on the use, by those known to react excessively to sunlight, of wide-brimmed hats and other protective clothing during the sunny months.

Summary

A comparatively common sensitivity to sunlight was observed among Chippewa Indians in Minnesota. The lesions constituted an overreaction to solar energy, with erythema, edema, vesiculation, and crusting. Many such patients develop a chronic impetigo, with brawny induration of the affected areas. The areas usually involved are the cheeks, nose, lower lip, ears, dorsal surface of hands, and the V-area of the neck. The condition characteristically appears during the spring and summer months and improves or clears completely with the onset of cold weather.

Because of the secondary protective changes brought about in skin by the use of methoxsalen combined with exposure to solar energy, a controlled trial of the drug was carried out during the months of July and August.

The condition of most patients improved during the period of hospitalization, but seven of the nine who did so had received the placebo. After having been discharged one week, there was a clear-cut distinction between patients who had received the placebo and those who had received the active drug. The condition of patients on methoxsalen therapy became worse in six, remained unchanged in three, and improved in none. Thus methoxsalen was found to exacerbate an already active dermatitis actinica. This was initially probably due to the known skin-sensitization response to sunlight induced by methoxsalen, together with the subsequent factor of inadequate control of exposure to sunlight because of the Chippewa Indians' unavoidable mode of living.

A further trial of methoxsalen might be of value in patients in early spring, prior to the activation of the dermatitis, to prevent or ameliorate the condition. However, a more practical preventive might be to encourage or to insist on the use, by those known to react excessively to sunlight, of wide-brimmed hats and other protective clothing during the sunny months.

1713 W. 105th St., Chicago 43.

The methoxsalen, supplied as Meloxine, and the placebo used in this study and reimbursement for photographic supplies and secretarial help were provided by the Upjohn Company, Kalamazoo, Mich.

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MANAGEMENT OF NONPENETRATING INJURIES OF THE CHEST

Claude C. Craighead, M.D.
and
Bertram A. Glass, M.D., New Orleans

In a series of 166 patients with nonpenetrating injuries of the chest there were 118 with fractures of ribs. Thirty-one of these were of the stove-in (flail chest) type, accompanied by paradoxical sinking-in of the chest wall during inspiratory contractions of the diaphragm. Sand bags sufficed to correct this dangerous condition in 9 patients, but in 19 it was necessary to apply traction either to the sternum or to the pectoral muscles. Immediate thoracotomy was resorted to on four occasions. Two patients with organized hemothorax and one with empyema required decortication. From this small number of complications it appears that early operation for nonpenetrating chest wounds is seldom indicated. Of eight deaths in this series only two were directly attributable to the injuries within the chest.

As various modes of travel are designed for higher and higher speeds, patients suffering blunt trauma to the chest, of frequent occurrence now, must be reckoned with in ever increasing numbers. It seems timely, therefore, to review the management and evaluate the results in an institution where many such injuries are seen. From July, 1954, through June, 1959, 166 patients having nonpenetrating injuries of the chest were admitted to the Thoracic Surgical Service, Louisiana State University Division, Charity Hospital, New Orleans.

Uncomplicated Fractures of the Rib

Patients with fractures of the rib treated in the outpatient clinic are not included in this study. However, 20 were admitted who had fractures of the rib without other complications. If an initial roentgenogram discloses no intrapleural complication, the patient is given analgesics and, frequently, intercostal nerve blocks to control pain. Another roentgenogram is made in six hours. If no intrathoracic lesion is demonstrable, the patient is usually sent home to return within 48 hours.

In one patient pneumothorax occurred two weeks after the initial injury and in one, hemothorax five days later. In three patients hemopneumothorax occurred after 2, 5, and 10 days respectively. Follow-up examination, therefore, is imperative.

Treatment of fractures of the rib by encircling devices is contraindicated. To splint a broken rib satisfactorily and relieve pain by strapping, the adhesive tape must be applied beyond the midline anteriorly and posteriorly. Respiratory excursion and, hence, efficiency are decreased, not only on the injured but also on the uninjured side. Complete encirclement of the chest by a belt decreases excursion on both sides. The sole benefit from such treatment is relief of pain. This can be more adequately controlled by intercostal nerve blocks repeated at 12-to-24-hour intervals, if necessary, without interfering with ventilatory function. Indeed, function is improved, since the patient is able to cough and breathe deeply without pain. The dangers of atelectasis and pneumonitis thus are minimized. Often the block affords prolonged relief from pain so that only a single injection is necessary. Rarely does a patient require more than four or five injections. It is advisable to inject two intercostal nerves above and two below the sites of fracture.

Although it is an infrequent sequel, pneumothorax may result from the needle puncture in carrying out the procedure. It is of minor significance if recognized and treated properly.

Subcutaneous Emphysema

Of interest in 13 patients with fractures of the rib was the occurrence of subcutaneous emphysema with neither pneumothorax nor hemothorax, a phenomenon sometimes difficult to interpret. In most instances previous pulmonary or pleural disease has been sufficient to cause visceral and parietal pleural symphysis. When an accident occurs, the jagged end of the rib penetrates underlying adhered lung to effect a small leak. The result would ordinarily be a pneumothorax. However, in cases in which adhesions underlie the site of injury, the air, having no pleural space to enter, escapes from the rent in the lung to dissect into the subcutaneous tissues. At times subcutaneous emphysema, without any other evidence of intrapleural injury, may be marked. Most instances resolve spontaneously but should be observed by serially performed roentgenography. Adhesions beneath the site of puncture may be thin and later tear to allow leakage of air and blood into the pleural space. Probably this mechanism obtained in several cases of delayed pneumohemothorax.

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the Department of Surgery, Louisiana State University School
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Subcutaneous emphysema is produced in yet another, and even more important, manner. Air escapes through an opening in a major bronchus, trachea, or esophagus, makes its way into the mediastinum, and progresses from there into the subcutaneous tissues. Thus evolves a critical situation, in which prompt discernment of the underlying disorder is demanded. If the leak is considered to be of sufficient magnitude to compress the great veins within the semiclosed mediastinal compartment and encroach on the return flow of blood to the heart, decompression is accomplished by opening the anterior mediastinum through a suprasternal approach. If the leak continues unabated and respiratory function is appreciably embarrassed, a large opening is present which calls for immediate surgical intervention to secure its closure.

Hemopneumothorax

Twenty-six patients had fractures of the rib associated with unilateral pneumothorax, 1 with bilateral pneumothorax, 30 with unilateral hemothorax, 23 with unilateral hemopneumothorax, and 1 with bilateral hemopneumothorax. Treatment in such cases must encompass one major goal, to rid the pleural space of fluid and air so that the visceral and parietal pleurae are apposed. The quickest way to stop the spill of air or blood from the lung is to secure contact of pleural surfaces, a principle long familiar to thoracic surgeons.

Blunt trauma rarely causes injury to major vessels. In any event, the few patients with bleeding from such sources will seldom live to be transported. Most intrapleural bleeding occurs from the peripheral lung, usually from puncture by a fragment of rib, and can be controlled by pleural apposition. Occasionally bleeding from an intercostal vessel cannot be checked by pleural coaptation. However, it is significant that open thoracotomy was undertaken only twice for uncontrolled bleeding, originating from intercostal vessels in both instances. Only two patients with clotted hemothorax required decortication.

The maintenance of a lung in collapse in order to seal a hole on its surface is not, in our opinion, to be countenanced. While it is true that the opening may eventually seal off and that the lung will reexpand as air is absorbed, there are several dangers. A pleural effusion of varying degree ensues. Unless the lung reexpands quickly, fibrinous exudate is deposited over its surface and soon organizes into a fibrous rind, entrapping the lung and preventing its reexpansion. Frequently the effusion becomes secondarily infected and empyema results. Empyema occurred in two patients with pneumothorax who were not seen until two or more weeks after their initial injury. One required decortication.

Pleural apposition may be accomplished in a variety of ways. A single aspiration served to accomplish this in 28 patients, while multiple aspirations were needed in 40. Use of tube thoracotomy was necessary in 47.

In pneumothorax alone, aspiration is the preferred method of treatment. An 18-gauge or 20-gauge needle is attached to a three-way stopcock; a large syringe is introduced into the second intercostal space in the midclavicular line and the air is drawn off. In a patient with pneumothorax with less than 15% collapse, aspiration is not done. Minimal pneumothorax will clear so rapidly that no pleural effusion develops. Conversely, complete collapse of the lung under obvious tension denotes a large leak. Treatment consists of immediate insertion of a catheter into the second intercostal space anteriorly and connected via a water trap to either the Emerson or Thoracic Gomco suction apparatus.

No single method is best for cases which fall between these two extremes. When possible, aspiration with a needle is preferable. Single or even multiple thoracenteses are less painful than insertion of an intercostal catheter which, although more efficient in emptying the pleural cavity, is invariably irritating to the pleura and causes pain on deep inspiration and coughing. Burdened with a tube, the patient breathes less deeply and coughs less. As a result atelectasis may develop. In addition, the danger of introducing infection into the pleural space, while slight in either case, is less with a needle than with a tube. There need be no hesitation, however, in use of a tube in those not responding quickly to aspiration.

In hemothorax, pneumothorax, or hemopneumothorax of moderate degree, an attempt is made to remove all air and fluid by performance of thoracentesis. If no negative intrapleural pressure develops after 500 cc. of air or more is removed and air continues to be drawn out, the leak is obviously large and an intercostal catheter is placed in at once. The pneumothorax machine is of value in determining intrapleural pressure in such cases. Similarly, if 500 cc. or more of blood is removed, or if the blood appears fresh some hours after injury, a catheter placed through the seventh or eighth intercostal space in the posterior axillary line affords the opportunity of a minute-to-minute check on the rate of bleeding, once the initial accumulation has been removed. The tube should never be placed more posteriorly than the posterior axillary line so that the patient may lie in comfort on his back.

In the patient on whom aspiration has been performed and who is thought free of fluid and air, an immediate portable roentgenogram is made with the patient in the upright position. If air persists, a tube is put in the second anterior interspace; if blood remains, it is placed in the seventh intercostal space at the posterior axillary line. If both air and blood are still accumulated, catheters may be placed anteriorly and posteriorly, or a multiperforated catheter may be introduced from the dependent portion and directed toward the apex.

If the roentgenogram is clear after thoracentesis, another is obtained in six hours. The degree of either pneumothorax or hemothorax at this time will decide whether thoracentesis is to be repeated or evacuation by catheter planned. During the period of observation, indicated diagnostic and therapeutic measures are carried out.

Performance of open thoracotomy was resorted to immediately on four occasions. Two patients with organized hemothorax and one with empyema required decortication. It would seem evident from this small number of complications, therefore, that early operation for nonpenetrating wounds is seldom indicated.

Other Injuries

Diaphragmatic Rupture.—Four patients with fractures of the rib and one with flail chest had associated diaphragmatic injury. Diaphragmatic rupture, per se, does not constitute an indication for emergency thoracotomy. Two patients, submitted to immediate thoracotomy, were considered to need emergency procedures because of associated conditions. One had severe respiratory distress and a massive diaphragmatic hernia, the left side of the chest being completely filled by abdominal viscera. His was one of the operative deaths and at autopsy the brain was extensively lacerated. This, no doubt, contributed more to the respiratory distress than did the diaphragmatic rupture. The second, operated on because of continued bleeding, had a herniation of the spleen through the diaphragm; the splenic pedicle was also lacerated.

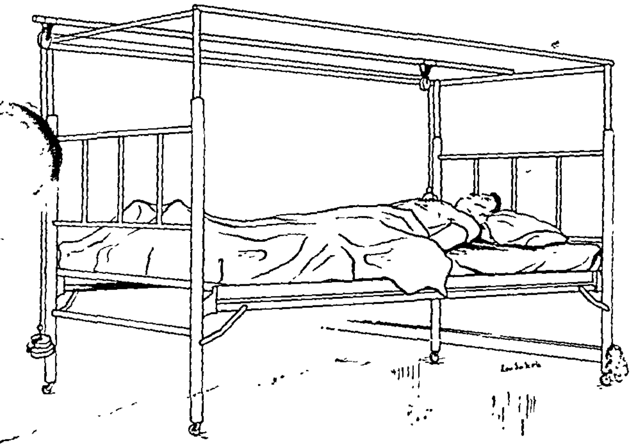

Fig. 1.—Stabilization of flail chest by sternal traction. Application of traction to sternum involves use of overhead frame.

Usually concomitant injuries such as pneumothorax or hemothorax can be treated and repair to the diaphragm delayed until the patient has recovered from the secondary injuries and his condition has been stabilized. Thee of five patients with ruptured diaphragm had synchronous craniocerebral trauma.

Mediastinal Injuries.—Four patients with fractures of the rib and two patients with flail chest had mediastinal damage. Three injuries involved the heart (definite myocardial infarct in two and questionable infarct in one) and one the tracheobronchial tree. In blunt injuries to the anterior chest wall, particularly those caused by steering wheels, the sternum is driven inward and presses the heart between it and the vertebral column. The myocardium is contused, and the clinical picture is that of a myocardial infarct. Consequently, any injured patient in whom the possibility of sternal compression exists should have serial electrocardiograms, and, if the myocardium is damaged, the patient should receive treatment as prescribed for myocardial infarction, as well as for his other injuries.

Sternal Fractures.—In 10 patients with fractures of the sternum, 2 also had hemothorax, 1 had myocardial injury, and 2 exhibited a marked paradoxical sinking-in of the chest wall during the inspiratory contractions of the diaphragm. In one patient the soft tissues overlying the sternum were contused without a demonstrable fracture of the sternum. Treatment of sternal fracture is similar to that of a broken rib. If no intrapleural or mediastinal injury exists, treatment is directed toward relief of pain.

Flail Chest.—More urgent than the previously described conditions, a crushing injury of sufficient magnitude to produce a flail chest demands an understanding of the resulting marked derangement of cardiopulmonary function for proper management. Of 31 patients with flail chest, 7 had associated hemothorax, 2 pneumothorax, 7 hemopneumothorax, 1 diaphragmatic rupture, and 2 myocardial injury.

It is of the utmost importance, when dealing with the stove-in (flail) chest, to stabilize the chest cage and to end the sinking-in of the injured part during each inspiration. Sand bags were used in 9, while traction from the sternum with Bigelow screws (fig. 1 and 2) [1] or from the pectoral muscles as described by Hudson,[2] or a combination of the two, was used in 19 patients. In the others the sinking-in was either minimal or else in a posterior location where rest in bed sufficed to splint the segment. Most of these cases have been reported elsewhere and treatment discussed in detail.[1]

Tracheotomy, of prime importance in the management of many thoracic wounds, is particularly advantageous in the management of patients with flail chest. While tracheotomy serves its most useful function as a means by which tracheobronchial secretions may be aspirated in the patient who cannot or will not cough, it also serves to lower the amount of dead air space and lessen the amount of physical work involved in respiration. Nasotracheal aspiration and bronchoscopy are frequently used to keep the tracheobronchial tract free of secretion.

Miscellaneous Injuries.—Other cases include one patient with mild intrapulmonary hemorrhage and one with hematoma of the chest wall, both of whom were treated symptomatically with good results.

Concomitant Injuries to Other Organs: Most concomitant injuries to other organs result from violent trauma and multiple injuries are frequent. Eleven patients had, in addition to the chest injury, injuries to the abdomen; 16 to the brain and spinal cord; 28 to bones and joints; and 4 to the genitourinary tract (table 1). Of the 59 concomitant injuries, 30 patients had involvement of one other system, 10 of two systems, and 3 of three systems (table 2). This points out the necessity of attention to all injuries. Treatment of the thoracic condition should not be emphasized to the point that care of other injuries is neglected (table 3).

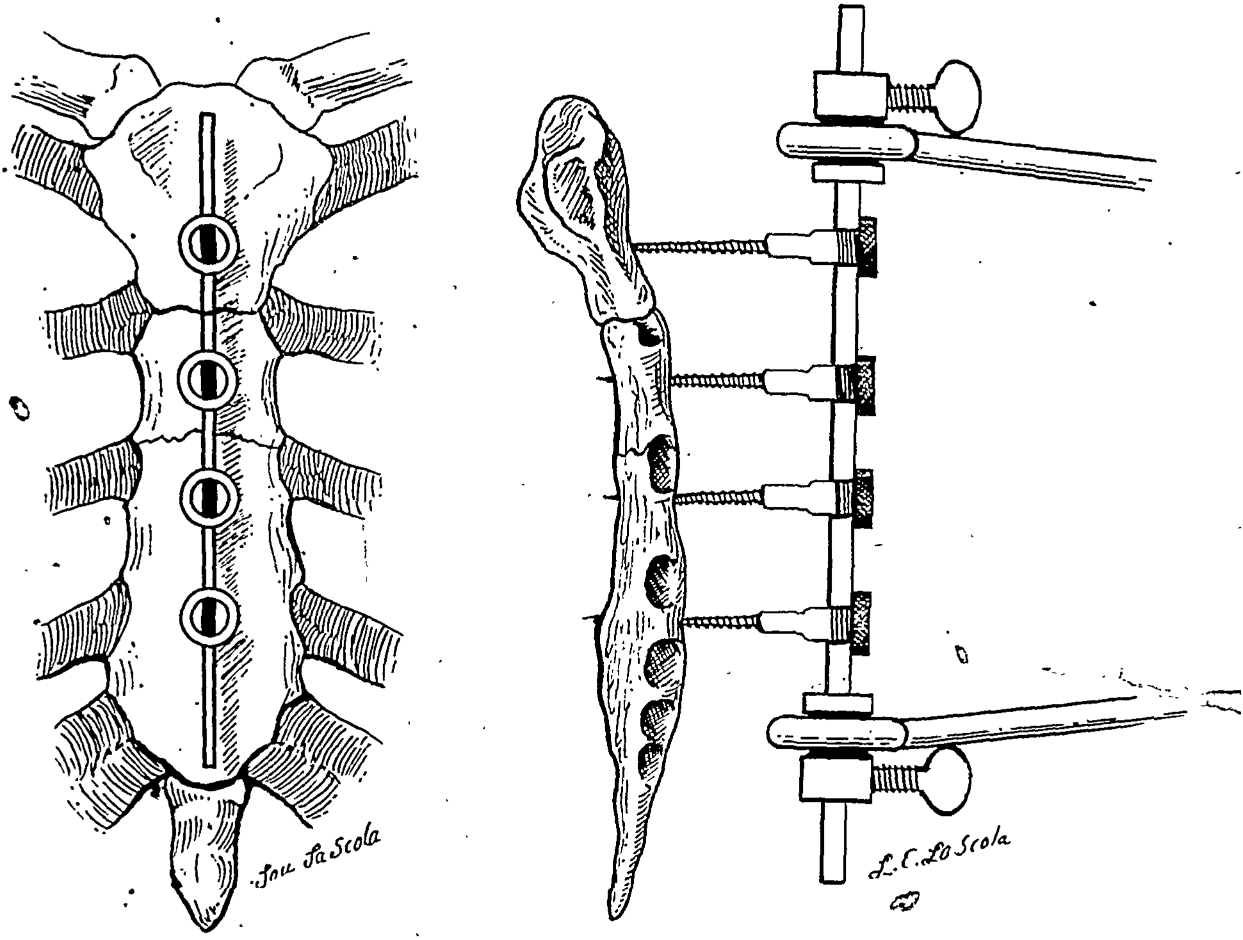

Fig. 2.—*Right,* diagrammatic sketch of fractured sternum with Bigelow screws and bar in place. Note two screws above and two below fracture site. *Left,* lateral view of sternum with Bigelow screws, bar, and traction clevis.

Deaths

Of the eight deaths, two were due to injury within the chest. The first was in a 55-year-old man with left hemopneumothorax and fractures of the femur and fibula, treated with repeated thoracenteses, tracheotomy, and closed reduction of the fractures. He developed acute pulmonary edema and died 48 hours after admission. Permission to perform autopsy was not obtained. The second was one of two operative deaths. A 28-year-old man was admitted after an automobile accident with multiple fractures of the rib, left hemopneumothorax, and intraperitoneal bleeding. Immediate treatment consisted of single thoracentesis followed by insertion of an intercostal catheter and tracheotomy. Thereafter, at exploratory celiotomy a ruptured spleen was removed and a contused kidney necessitated drainage of the renal fossa. The patient died 48 hours later as a result of, according to the findings at autopsy, acute myocardial infarction, presumably due to trauma and cerebral contusion.

Four deaths were ascribed to other injuries. Three were from cerebral lacerations, and fractures of the rib were incidental. The fourth was also adjudged due to cerebral laceration. This death was previously discussed in the section on diaphragmatic rupture.

Of the two other deaths, one occurred in a 65-year-old woman with fractures of the rib who died of a pulmonary embolus eight days after admission. The second occurred in an 87-year-old man with known cardiac disease. Admitted with fractures of the rib, he developed cardiac failure and died with acute pulmonary edema two weeks after admission.

Comment

Of 118 patients with fractures of the rib, 20 demonstrated no other lesion. Thirteen patients developed subcutaneous emphysema. The rest collected either air or blood, or both, in one or both of the pleural cavities. Four received, in addition, a tear in the diaphragm.

Ten patients suffered fractures of the sternum and one a contusion of the sternal region without evidence of fracture. Thirty-one patients exhibited, as a prominent feature, a flail chest. One patient had an intrapulmonary, and another a subcutaneous, hematoma.

Table 1.—*Associated Lesions in Patients with Nonpenetrating Chest Injuries*

Type of Lesion	Patients, No.
Abdominal Injuries	
Spleen	3
Spleen and pancreas	1
Spleen and liver	1
iver	2
dynamic ileus	4
Total	11
keletal Fractures	
Pelvis	3
Vertebra	3
Mandible	3
Clavicle	3
Upper Extremity	8
ower extremity	8
Total	28
Craniocerebral and spinal	
Concussion	10
Depressed skull fracture	1
Cerebral laceration	3
Severed spinal cord	1
Basilar fracture	1
Total	16
Genitourinary	
Fracture of kidney	1
Hematoma of kidney	1
Cord bladder	1
Hematuria	1
Total	4

Complications immediately attributable to the thoracic injury included three instances of organized hemothorax and three of empyema; two patients with the former and one with the latter were treated by decortication. Atelectasis was severe enough in 16 patients to require use of bronchoscopy and in 9, of tracheal suction. Pneumonia occurred in seven patients. A myocardial infarct developed in one patient and pulmonary edema and electrolytic imbalance in another.

Treatment in 42 patients consisted solely of supportive care, including in many instances, intercostal nerve block. The less formidable thoracentesis sufficed for accumulations of air and blood in the pleural cavity in 68 patients, while the more efficient intercostal drainage was required for larger collections in 47 patients. To remove air, the needle or catheter was put in the second anterior interspace and to drain off blood, in the seventh posterolateral space. Some modification of these approaches was demanded in patients with pocketed accumulations.

Table 2.—*Distribution of Involvement of Other Organ Systems*

Systems, No.	Patients, No.
One	
Abdominal	3
Skeletal	18
Craniocerebral-spinal	9
Two	
Abdominal, craniocerebral-spinal	1
Abdominal, skeletal	4
Abdominal, genitourinary	1
Genitourinary, skeletal	1
Skeletal, craniocerebral-spinal	3
Three	
Abdominal, craniocerebral-spinal, genitourinary	1
Abdominal, skeletal, craniocerebral-spinal	1
Skeletal, craniocerebral-spinal, genitourinary	1

In 9 patients with flail chest the placement of sand bags on the involved segment relieved their symptoms, and in 19 patients sternal or pectoral traction was necessary. Tracheotomy was performed on 19 patients. In four patients the chest was explored shortly after admission.

3636 St. Charles Ave. (15) (Dr. Craighead).

Table 3.—*Treatment of Associated Injuries*

Type of Treatment	Patients, No.
Supportive care only	28
Exploratory celiotomy	6
Transthoracic splenectomy	1
Closed reduction of fractures	15
Open reduction of fractures	4
Cranial trephination	2
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DIAGNOSIS OF INTERMEDIATE STAGE OF ALCOHOLIC BRAIN DISEASE

Abram E. Bennett, M.D., Berkeley, Calif.

Between the acute, reversible forms of alcoholic brain disease and the chronic, irreversible forms exemplified in cortical atrophy, there is an intermediate group of forms in which severe disturbances of the personality are present, but permanent organic deterioration can still be prevented. This belief, based on clinical impressions, is strengthened by electroencephalographic studies in 227 patients. Of these, 81 were classified as intermediate by clinical criteria, and 64 of the 81 had abnormal electroencephalograms which reverted slowly to normal. Five case histories illustrate the type of personality change encountered, the difficulty of management, and the need of resolute treatment if patients still in the intermediate, reversible stage are to be saved from irremediable cortical atrophy.

Alcoholic brain disease has been classified as either acute alcoholic brain syndrome, acute intoxication, delirium tremens, and acute hallucinosis (reversible) or as chronic brain syndrome, cortical atrophy, and midbrain involvement (organic dementia or Korsakoff's or Wernicke's disease [irreversible]). From my studies I believe that large numbers of chronic alcoholics lie between these groups and have what I term the intermediate brain syndrome; this paper presents the evidence for this concept.

An increase in the incidence of alcoholic brain damage throughout the United States is shown by many indications; for example, the increasing number of admissions to state hospitals, of which about 20% are for alcoholism, either with or without definite psychoses. In electroencephalographic studies of 758 (512 male, 246 female) alcoholic patients admitted to the psychiatric department of a private general hospital over the past six years, I have found at least one-third with abnormal recordings, many of which reverted to normal only after many months of sobriety.[1] These patients are in either the intermediate or the chronic stage of organic brain disease, in both of which cortical cerebral atrophy is present. If the diagnosis can be made in the intermediate stage, permanent organic deterioration may be prevented. I believe that thousands of these cases go unrecognized.[2] The patients have reached the phase of the essential pathology of chronic alcoholism; namely, compulsive drinking with permanent loss of control over drinking.

Heretofore the symptoms in this group were largely considered to be emotional personality changes, either sociopathic or neurotic disorders, to be treated psychotherapeutically; whereas one can now demonstrate that these are signs of organically induced cortical damage, more like frontal lobe syndromes. In those patients with slow reversal of abnormal electroencephalograms (EEG's) or persistence of abnormal records, the organic basis has been confirmed by psychological testing and by pneumoencephalography which reveals cortical atrophy. The degree of cortical atrophy roughly parallels the clinical and electroencephalographic findings. To be sure, some persons with chronic cases and with severe atrophy have normal electroencephalographic patterns; the same thing was seen in the past in treated cases of advanced paretic dementia[3] and also in some hopeless cases of Korsakoff's disease.

Electroencephalographic Studies in 227 Patients with Alcoholism

The electroencephalographic findings in general are persistent mild generalized activity of 15 to 30 and 4 to 7 waves per second and at times paroxysmal slowing and spiking. Of the 227 patients studied 78, or 34.4%, had two or more electroencephalograms; 25, or 11%, had psychological tests; and 12, or 5.3%, had pneumoencephalograms. Findings on the repeat EEG's are shown in the table.

Acute Stage.—Of 98 patients with alcoholic brain disease in the acute stage, 37 had abnormal EEG's which reverted to normal. Psychological testing was done in eight cases and in three showed evidence of organic brain damage. The EEG's were normal in 53 cases.

Intermediate Stage.—Sixty-four (79%) of 81 patients with disease in the intermediate stage had abnormal EEG's, which usually reverted to normal slowly. On psychological tests, five of six patients showed organic brain damage, while three of four patients had pneumoencephalograms that showed cortical atrophy. EEG's were normal in 17 cases.

Chronic Stage.—There were 48 patients with disease in the chronic stage. Of these, 38 (79.2%) had abnormal EEG's. All 11 patients given psychological tests had evidence of organic brain damage. Pneumoencephalograms in seven of eight patients showed cortical atrophy. There were normal EEG's in 10 cases.

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Heretofore the symptoms in this group were largely considered to be emotional personality changes, either sociopathic or neurotic disorders, to be treated psychotherapeutically; whereas one can now demonstrate that these are signs of organically induced cortical damage, more like frontal lobe syndromes. In those patients with slow reversal of abnormal electroencephalograms (EEG's) or persistence of abnormal records, the organic basis has been confirmed by psychological testing and by pneumoencephalography which reveals cortical atrophy. The degree of cortical atrophy roughly parallels the clinical and electroencephalographic findings. To be sure, some persons with chronic cases and with severe atrophy have normal electroencephalographic patterns; the same thing was seen in the past in treated cases of advanced paretic dementia[3] and also in some hopeless cases of Korsakoff's disease.

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Clinical Observations and Symptoms

Personality changes in persons with intermediate-stage brain damage include rationalization of drinking, pathological lying, infantile behavior, poor judgment, hostility, emotional lability, and lack of insight. The drinking pattern is addictive, dependent, or compulsive, usually with daytime and solitary drinking. Among physiological reactions are included blackouts, withdrawal reactions, and severe hangovers. There are delirious or convulsive episodes in about 50% of cases and systemic complications such as fatty liver, cirrhosis, and polyneuritis. On psychological tests the main findings are perceptual (visual) organization defect, intellectual and personality deterioration, and impaired power of abstraction.

Since I started my investigations I have discovered a study done in France by Lafon and others[4] that confirms my findings. They compared electroencephalographic and pneumoencephalographic studies in 100 cases of chronic alcoholism; the pneumoencephalograms revealed cerebral atrophy in 78 of the 100 cases. In 8% the atrophy was cortical, in 44% subcortical, and in 48% cortico-subcortical. No strict correlation between the degree of atrophy and the clinical manifestations was observed. Of the 100 patients, 80 had abnormal and 20 normal EEG's. In 58 patients the findings of pneumoencephalograms and EEG's could be definitely correlated. In 42 patients radiologic findings of atrophy were significant but the EEG's were within normal limits.

*Findings on Repeat Electroencephalograms in Seventy-eight Cases of Alcoholic Brain Disease**

	Acute	Intermediate	Chronic
Decreased abnormality	13	21	6
Unchanged	2	14	14
Increased abnormality	0	4	4
Totals	15	39	24

* Two or more repeat EEG's.

It is hard to determine accurately from the clinical picture alone just what phase of alcoholism the patient is in and what developing symptoms point to permanent brain damage. A significant early symptom is the appearance of blackouts or temporary periods of amnesia about happenings during drinking; this symptom usually means that brain disease from alcohol is either present or near. Irreversible brain change will begin possibly within a year or two after the development of recurrent blackouts. The phase of increasing dependency on alcohol and inability to control drinking forces the drinker into intricate rationalizations, alibis, and lies about his drinking, aptly called "alcoholic thinking" by Alcoholics Anonymous. Anyone in this phase should be considered to be suffering from progressive impairment of frontal lobe brain functioning. The drinking pattern is usually compulsive, with solitary and daytime drinking. Intellectual impairment continues, with poor judgment, emotional lability, infantile behavior, hostility, defiance and denial of illness, and complete lack of insight as part of the clinical picture. Too often these symptoms are considered to be due to the sociopathic personality of the alcoholic, whereas they are determined by the chronic toxic effects of the addictive drug ethyl alcohol and are organic symptoms of brain damage.

Report of Cases

Case 1.—A 45-year-old man, who had been a solitary drinker for the previous two years, drank up to a quart of vodka daily. He had lost 50 lb. (22.7 kg.) in one year and had had attacks of polyneuritis for the previous year. Personality change, general loss of interest, errors in business judgment, and occasional blackouts were his symptoms during the two years. An EEG and psychological tests were normal, spinal fluid findings were normal, there was 8% retention of sulfobromophthalein, and a pneumoencephalogram showed enlarged subarachnoid spaces and basilar cisterns, widened cortical pathways, and slight ventricular enlargement.

Case 2.—The patient, a man 50 years of age, had been an excessive, compulsive drinker for three years. At his first admission he had acute delirium followed by two convulsions. An electroencephalographic recording was distinctly abnormal, with slow activity, superimposed fast activity, and spike discharges; repeated records showed the same pattern. On a second hospitalization 18 months later for acute intoxication without delirium, his recording was still abnormal. He was given disulfiram and his drinking was controlled for the next two years, at the end of which his electroencephalographic pattern became normal. It has remained so for another four years.

Case 3.—A man, aged 45, had been a social drinker since college days. After discharge from the Army, after marital discord and divorce, he began excessive and compulsive secretive drinking. He had remarried, and for two years before his admission he had had temper outbursts and rages and had physically abused his wife. Even small amounts of alcohol produced blackouts and irrational periods, and his wife had to watch over him constantly. Psychotherapy was tried for months, and he joined Alcoholics Anonymous, but with little change in personality or behavior. He agreed to hospital care when his wife threatened to leave him. Two EEG's were normal. A battery of psychological tests was diagnostic of neurotic character disorder, with diffuse organic impairment defect in immediate memory, some concreteness in thinking, and a disturbance in his visual spatial organization. The pneumoencephalogram showed mildly dilated ventricles, dilated basal cisterns, and dilation of all the subarachnoid spaces—suggestive of brain atrophy. This patient now takes disulfiram daily and has remained abstinent for two years. He is successful in both his home life and his business.

Case 4.—A woman, aged 49, had drunk excessively for many years and had had violent episodes with extreme hostility toward her family. From time to time she would have convulsive seizures during her drinking. During her first hospitalization she denied having any problems and blamed her family entirely for all her difficulties. Three EEG's taken during her three weeks' stay in the hospital were all abnormal, with slow activity and moderately fast activity. The patient continued to drink after discharge, and on her second hospitalization two years later she was very demonstrative and euphoric or expansive; she had a grand mal convulsive seizure on the fifth day, followed by two days of delirium. An EEG taken at this time, just before the delirious episode, showed the same severe fast activity. Psychological tests during this period of hospitalization showed evidence of definite organic impairment. Pneumoencephalograms made elsewhere during a prior hospitalization showed evidence of brain atrophy.

Case 5.—A man, aged 49, had been a problem drinker for 20 years. Presumably his drinking contributed to marital difficulties, and in a few years his wife left him. He had lost many jobs because of drinking, but his father's influence had always helped him to find new work. After the father's death in 1954, the patient lived alone with his mother. He drank almost continuously except for periods when his mother took him on trips. He had been in contact with Alcoholics Anonymous since 1949, and in recent years had gone to meetings quite regularly but continued to drink. While living with his mother the patient tried to conceal his drinking from her, and she in turn acted constantly as a watchdog and nurse. During periods of drinking he would become ugly and sarcastic, telling his mother he despised her; on one occasion he physically abused her and almost killed her. In 1954, after he had lost a job because of drinking, he was committed to a state hospital for three months. On discharge, he took a trip abroad and impulsively, on short acquaintance, married again without having previously obtained a divorce.

At the insistence of his mother and through the influence of Alcoholics Anonymous, he was finally brought in for evaluation. The patient was an overly familiar, very pleasant, passive man. Although he admitted all of his difficulties with drinking, he minimized their importance and had no insight into the seriousness of his condition. He felt he could do all right if he could move to his own apartment away from his mother. He saw no reason why he should either stop drinking or attempt to find useful work. He readily agreed to go along with my recommendations but it was quite obvious that he could not carry them out.

An electroencephalogram revealed a distinctly abnormal record with a mixture of slow waves and fast activity. A variety of psychological tests showed a generalized deterioration of his personality functioning, with evidence of organic factors and defects such as confusion and memory impairment, all suggesting serious brain damage. On pneumoencephalographic study, it was found that he had almost twice the normal amount of cerebrospinal fluid and there was marked enlargement of the entire ventricular system and patchy evidence of brain atrophy. He made no improvement and had to be committed to a state hospital.

Therapeutic Implications

It is important to recognize the intermediate stage of alcoholic brain disease because the usual therapeutic program must be changed. These patients first need medical care until the organic features of brain damage clear sufficiently for them to be able to gain insight. In 50% of cases it usually means treating other systemic disease, such as liver damage, and may take from weeks to months. Education of relatives as well as of the patient is important, and the significance of brain damage must be explained. Relatives are more tolerant of patients' personality changes and unusual behavior if they understand that much of it is beyond their control but that through prolonged treatment the organic features will improve.

All of these patients require either restraining care, through prolonged hospital or institutional control, until some insight can be established or a combination of close supervision at home to prevent access to alcohol and the judicious use of disulfiram or calcium carbamide to prevent drinking. An inviolate principle in treatment must be that alcoholics with disease in this stage must abstain from use of alcohol absolutely and permanently.

Even though our patients are informed of the seriousness of alcoholic brain damage, they are especially difficult to treat and may continue drinking. Some die of intercurrent disease or by suicide or require permanent institutional care. If control can be established until the organic features clear and fairly normal judgment returns, the beginning of insight can be established and the motivation to learn to live without alcohol can be developed. Psychiatric evaluation to determine whether the alcoholism is symptomatic of a neurosis or psychosis must also be considered.

After the patient gains some insight, psychotherapeutic efforts may be fruitful, along with social and other supportive measures such as membership in Alcoholics Anonymous, to bring about effective rehabilitation. I have described my overall treatment program elsewhere.[5]

Conclusions

In the syndrome of the intermediate stage of alcoholic brain disease the electroencephalographic changes and the clinical and psychological findings lead to the diagnosis. Pneumoencephalographic examination will confirm the presence of cerebral atrophy. The organic features of these cases are often erroneously considered to indicate emotional personality disorders. The recognition of this stage is of extreme importance prognostically and therapeutically.

2000 Dwight Way.

Valuable assistance in this research was given by Larry Mowrey, L. T. Doi, M.D., and Joel Fort, M.D.

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ADAMS-STOKES SYNDROME ASSOCIATED WITH CHRONIC HEART BLOCK

TREATMENT WITH CORTICOSTEROIDS

Charles K. Friedberg, M.D., Melvin Kahn, M.D., James Scheuer, M.D., Selvyn Bleifer, M.D.
and
Simon Dack, M.D., New York

The authors report on six patients in whom prednisone therapy either permanently or temporarily diminished or eliminated heart block and abolished the associated attacks of syncope. The attacks were eliminated within 24 hours after the beginning of corticosteroid therapy, whether or not the heart block was alleviated. The case histories illustrate the relief afforded by prednisone, the recurrence of heart block when dosages were reduced or interrupted, the occasional absence of symptoms in the presence of recurrent heart block, and the occasional failure of the patient to respond further to dosages of prednisone that had previously been effective. The drug was given in doses of 60 mg. per day initially, and it was not always possible to reduce the dosage to 30 mg. without a return of the syndrome. Prednisone sometimes was effective after atropine and isoproterenol had failed, and no untoward results followed the simultaneous administration of all three drugs.

Despite the availability of a variety of therapeutic agents, the treatment of Adams-Stokes syndrome associated with heart block is often unsatisfactory and the prognosis ominous. The sympathomimetic amines, isoproterenol hydrochloride and epinephrine,[1] and external or internal electrical artificial cardiac pacemakers[2] have been used most commonly and with variable degrees of success.[3] Although their use has often been lifesaving, their effectiveness is commonly of temporary duration. The sympathomimetic drugs must be given intravenously and the dosage carefully and continuously adjusted. The use of a cardiac pacemaker requires complex equipment which is not always readily available and has other disadvantages. Among other agents which have been used, atropine is generally ineffective, and the value of sodium lactate has not been adequately confirmed. The use of the latter is associated with the danger of serious arrhythmias and congestive heart failure. Because of the poor prognosis for patients with Adams-Stokes syndrome and the shortcomings of commonly used therapy, it appears desirable to call attention to additional therapeutic agents, the corticosteroids. The purpose of this report is to present some encouraging experiences with the use of the drugs in six patients with Adams-Stokes syndrome and heart block, in whom prednisone therapy was either permanently or temporarily capable of abolishing the seizures and of diminishing or eliminating the heart block.

From the Division of Cardiology, Department of Medicine, the Mount Sinai Hospital.

In single cases of heart block associated with acute myocardial infarction reported by Prinzmetal and Kennamer[4] and by Phelps and Lindsay[5] ACTH or cortisone therapy abolished the attacks and restored sinus rhythm within one to several hours. Rosenfeld and Segall[6] administered cortisone to two patients with Adams-Stokes syndrome and heart block. One died despite its use in conjunction with the external cardiac pacemaker, whereas in the other the attacks ceased soon after administration of cortisone. The use of an external pacemaker which previously had been necessary for 10 hours was no longer required. Tung and colleagues[7] terminated Adams-Stokes attacks in two patients with complete heart block within 24 hours after administering ACTH therapy. In three cases reported by Litchfield and co-workers[8] corticotropin controlled attacks in less than 24 hours. Jones[9] was able to prevent repeated attacks by the simultaneous administration of isoproterenol hydrochloride intravenously and 40 mg. of prednisone daily; the relative importance of the prednisone therapy is therefore uncertain.

Report of Cases

Case 1.—A 79-year-old man was admitted to the hospital on Sept. 26, 1958, because of a syncopal attack three weeks prior to admission and dizzy spells, dyspnea, and confusion since. The patient had mild diabetes of 30 years' duration. The night prior to admission there was an episode of acute pulmonary edema. An electrocardiogram revealed a varying 2:1 and 3:1 atrioventricular block (fig. 1*A*).

The patient was treated for congestive heart failure, and because of hemoptysis, possibly due to pulmonary embolism, therapy with anticoagulants was begun. Atropine, ephedrine, and isoproterenol (Isuprel) hydrochloride were ineffective in improving the degree of heart block. On the patient's 15th hospital day treatment with prednisone, 15 mg. four times daily, was begun. Thirty-six hours later, after the patient had received 90 mg. of prednisone, normal atrioventricular conduction was restored with the ventricular rate averaging 75 per minute (fig. 1*B*). Mental clarity returned and the patient became asymptomatic. On the 18th hospital day the administration of prednisone was abruptly stopped because of increased glycosuria. Seven days after therapy with prednisone had been discontinued there was a syncopal episode and an electrocardiogram revealed 1:1 and 2:1 atrioventricular conduction with the ventricular rate varying between 44 and 72 per minute (fig. 1*C*). Prednisone was again given and normal atrioventricular conduction was restored within 24 hours (fig. 1*D*). The patient was finally discharged from the hospital after 29 days, receiving 5 mg. of prednisone four times daily.

While the patient was at home complete heart block with Adams-Stokes attacks occurred three times concomitantly with an abrupt reduction in the prednisone dosage. Regular sinus rhythm was restored on each occasion within 24 hours after the reinstitution of prednisone therapy. The patient eventually died at home during an episode of acute pulmonary edema.

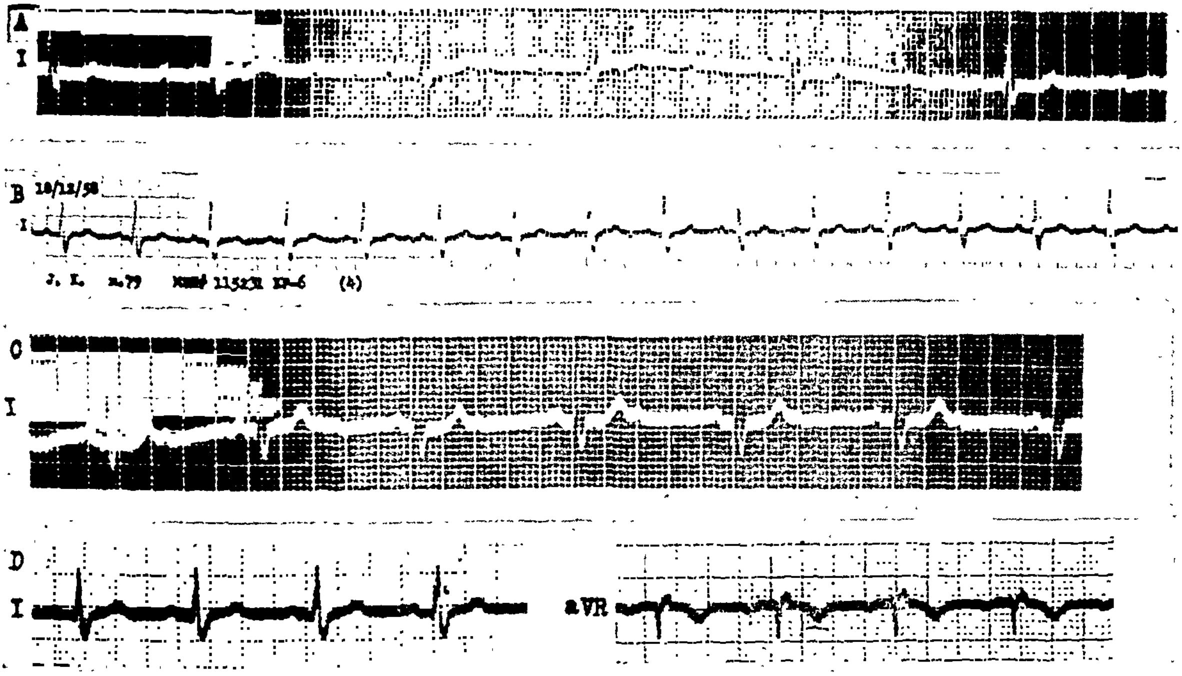

Fig. 1.—Electrocardiograms of patient in case 1. *A*, on admission of patient 2:1 and 3:1 atrioventricular conduction was present. *B*, 36 hours after the initiation of prednisone therapy normal atrioventricular conduction was present. *C*, seven days after cessation of prednisone therapy 2:1 atrioventricular conduction was present. *D*, 24 hours after reinstitution of prednisone therapy normal atrioventricular conduction was present.

Comment.—This case illustrates the prompt abolition of Adams-Stokes syndrome and the restoration of normal atrioventricular conduction within 12 to 36 hours on repeated occasions with prednisone therapy and reversion to heart block within several days after the cessation of therapy.

Case 2.—A 57-year-old woman was admitted to the hospital on May 5, 1958, because of syncopal attacks during the week prior to admission. She had been known to have hypertension for one year prior to admission for which she was treated with mild antihypertensive drugs. An electrocardiogram revealed a 2:1 atrioventricular block and periods of complete heart block and was suggestive of left ventricular hypertrophy. Roentgenographic examination disclosed enlargement of the heart.

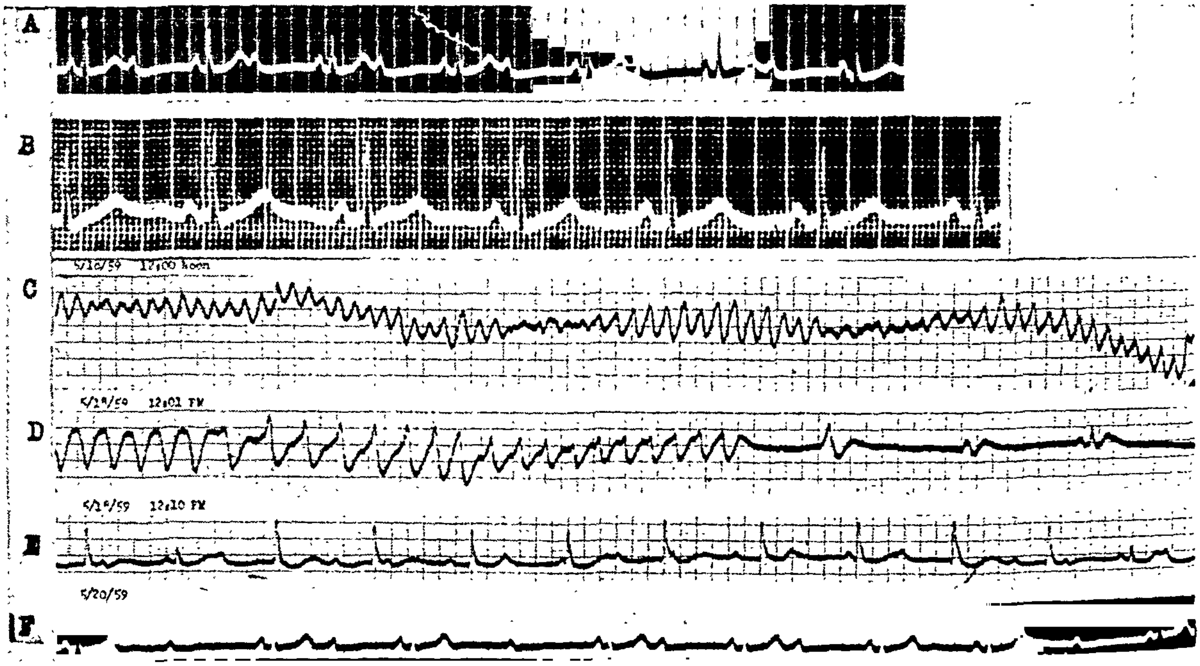

Fig. 2.—Electrocardiograms of patient in case 2. *A,* on patient's second admission to hospital 2:1 atrioventricular conduction was present. *B,* 16 hours after initiation of prednisone therapy normal atrioventricular conduction was present. *C* and *D,* shortly after patient received isoproterenol ventricular flutter, fibrillation, and tachycardia were present. *E,* 10 minutes after ventricular arrhythmia, complete heart block with occasional conducted beats was present. *F,* after episode of ventricular arrhythmia second degree heart block persisted.

On the second hospital day there was a generalized convulsive seizure which was associated with a slow heart rate and was treated with intramuscularly injected isoproterenol, atropine, and ephedrine. There were no further Adams-Stokes attacks, and after the patient was discharged she was given a long-acting isoproterenol preparation, but a 2:1 heart block still persisted. She was again admitted to the hospital Jan. 26, 1959, because of two syncopal attacks. An electrocardiogram revealed a 2:1 atrioventricular block (fig. 2*A*). With sublingual isoproterenol and atropine therapy the ventricular rate remained at 40 per minute. On the second hospital day there was a syncopal attack, and an electrocardiogram revealed a complete heart block, with a subsequent 2:1 atrioventricular block.

On the third hospital day therapy was started with 10 mg. of prednisone four times daily, and 16 hours later there was normal atrioventricular conduction (fig. 2*B*). Administration of atropine and isoproterenol was discontinued, and during the next several days there were occasional periods of 2:1 atrioventricular block and complete heart block but no syncopal attacks. On two occasions reduction of dosage of prednisone was followed by 2:1 heart block, and there was a return to normal conduction after the dosage was again increased. For the next 10 days there was alternation between 1:1 and 2:1 atrioventricular conduction, but the patient was asymptomatic. Therapy with prednisone was then discontinued and 2:1 and 3:1 atrioventricular block predominated. After therapy with long-acting isoproterenol but without prednisone 2:1 and 1:1 conduction remained the predominant rhythm and the patient was discharged.

On June 19, 1959, the patient was readmitted because of a syncopal attack. The electrocardiogram revealed complete heart block. Therapy was started with intravenously given hydrocortisone, atropine, and prednisone, 15 mg. four times a day. The next day there was an episode of ventricular arrhythmia shortly after the patient had received intramuscularly given isoproterenol (fig. 2*C, D,* and *E*). This reverted spontaneously to a normal sinus rhythm, followed by 2:1 and complete heart block. Thereafter the rhythm varied from normal atrioventricular conduction to second degree heart block (fig. 2*F*), and there were no further syncopal attacks. Administration of prednisone and atropine was discontinued and the patient was discharged on the 15th hospital day.

Comment.—This case illustrates the effectiveness of treatment with prednisone in abolishing syncope and restoring normal atrioventricular conduction after treatment with sympathomimetic amines had failed. Despite continued use of prednisone there was gradual reversion to a partial heart block, but syncope did not recur. One of the dangers (ventricular tachycardia or fibrillation) of sympathetic amine therapy was encountered.

Case 3.—A 58-year-old man was admitted to the hospital on July 16, 1958, because of several attacks of syncope during the preceding two weeks. There was no history of heart disease. The electrocardiogram showed a sinus arrhythmia at a rate of 70 per minute with 1:1, 3:2, and 2:1 atrioventricular conduction and a left bundle-branch-block pattern.

Despite large doses of atropine, isoproterenol, and ephedrine there was no change in the cardiac rhythm by the 10th hospital day. Use of all these medicaments, except isoproterenol, was discontinued. Administration of prednisone, 10 mg., three times a day, was begun. After two doses of prednisone normal atrioventricular conduction was present. The isoproterenol therapy was discontinued and the dosage of prednisone decreased to 5 mg. three times a day. On the 13th hospital day the patient was discharged on this regimen with normal atrioventricular conduction and without symptoms.

Administration of prednisone was discontinued three days after discharge, and normal conduction persisted for four months, until Nov. 11, 1958, when again episodes of dizziness without syncope were noted by the patient. An electrocardiogram showed complete heart block with occasional conducted beats and a ventricular rate of 40. Despite therapy with isoproterenol, atropine, prednisone, and molar lactate, complete heart block persisted. All medication was stopped and the patient was discharged with complete heart block. This rhythm persisted after discharge, but the patient remained asymptomatic.

Comment.—This case illustrates the effectiveness of prednisone therapy in restoring normal atrioventricular conduction and preventing Adams-Stokes attacks after treatment with the usual sympathomimetic amines had failed. In contrast to the preceding case, in this case the effect was long lasting. The refractoriness of the heart block to prednisone on a subsequent trial is also illustrated.

Case 4.—A 55-year-old man was admitted to the hospital on March 10, 1959, because of syncopal attacks. For the two years prior to admission he had been known to have partial heart block, and there were occasional episodes of syncope. For the week prior to admission there was a slowing of the pulse rate and more frequent syncopal attacks. The electrocardiogram showed a sinus rhythm with 2:1 and 3:1 atrioventricular conduction and a right-bundle-branch block pattern.

There was no change in the cardiac rhythm during therapy with isoproterenol and ephedrine. Treatment with these drugs was discontinued and administration of prednisone, 15 mg. four times a day, was begun. Sixteen hours after the first dose of prednisone was given 1:1 and occasional periods of 2:1 atrioventricular conduction were noted. On the seventh hospital day the dosage of prednisone was reduced to 40 mg. per day, and ephedrine, 25 mg. four times a day, was added. On the ninth hospital day the predominant conduction was 1:1 and the ventricular rate was 65. There were no further syncopal attacks and the patient was discharged on a regimen of 30 mg. of prednisone and atropine. The pulse rate soon decreased to between 32 and 40 per minute and the electrocardiogram showed 2:1 and 3:1 atrioventricular block. The patient remained asymptomatic, however. One month later, without any change in medication, the pulse rate became 80 and 1:1 atrioventricular conduction was noted. Despite the periods of varying atrioventricular conduction the patient had no Adams-Stokes attacks for the three months during which he received prednisone. For the previous two years there had been no period free of syncopal attacks of greater than one month's duration.

Comment.—This case illustrates the effectiveness of prednisone in abolishing Adams-Stokes attacks and in restoring normal atrioventricular conduction. There was a reversion to a partial heart block when dosage of prednisone was decreased but there was no recurrence of symptoms.

Case 5.—A 64-year-old man was admitted to the hospital on Dec. 22, 1958, because of syncope. Attacks had begun in May, 1958, and recurred with increasing frequency. An electrocardiogram revealed sinus rhythm with 2:1 and 3:2 atrioventricular block, a P-R interval of 0.22 seconds, and a right-bundle-branch block pattern.

With use of ephedrine and atropine therapy, normal atrioventricular conduction was restored. On the 10th hospital day the patient developed bronchopneumonia with a temperature of 104 F (40 C). This was followed by several Adams-Stokes attacks and complete heart block. From this time on the patient was monitored by a pacemaker (Electrodyne model PM-65). Electrical stimulation was used during the syncopal attacks, which were all due to periods of asystole. With antibiotic therapy the fever had abated but the attacks continued despite isoproterenol therapy. On the 16th hospital day there was a syncopal episode during micturition. Therapy with isoproterenol was discontinued and administration of prednisone, 60 mg. per day in divided doses, was begun. No further syncopal attacks occurred. The next day 2:1 atrioventricular block was the predominant cardiac rhythm, and after four days normal atrioventricular conduction was present.

Three attempts were made to abruptly reduce the steroid dosage to less than 60 mg. per day. Each attempt was soon followed by Adams-Stokes attacks, and these were promptly abolished by reinstitution of the original dosage level. After several weeks, however, the patient developed complete heart block with rare Adams-Stokes attacks despite continued prednisone therapy.

Comment.—This case illustrates the repeated effectiveness of prednisone therapy in the abolition of Adams-Stokes attacks; an apparent dosage dependence for these effects; and the development of refractoriness to dosages of prednisone that were previously effective.

Case 6.—A 57-year-old woman was admitted to the hospital on June 8, 1958, because of a convulsion. An electrocardiogram revealed complete heart block with multifocal ventricular contractions and a ventricular rate of 36 to 40 per minute. Therapy with large doses of atropine and isoproterenol for three weeks failed to significantly reduce the frequency of Adams-Stokes attacks.

She was then given hydrocortisone, 50 mg. intramuscularly, and prednisone, 10 mg. every six hours. The other medications were continued without change. During the 36 hours after the administration of hydrocortisone she had four mild syncopal episodes with convulsions, but thereafter she was free of symptoms. The complete heart block persisted with an unchanged regular idioventricular rhythm. On July 9 the dosage of prednisone was reduced to 30 mg. daily, and the next day the patient had a short syncopal episode. She was discharged from the hospital on July 11 receiving prednisone, 40 mg. daily, atropine sulfate, 0.4 mg. three times daily, and isoproterenol, 5 mg. sublingually every four hours. At the time of this writing she has had regular sinus rhythm without heart block, and the dosage of prednisone has been diminished to 15 mg. daily.

Shortly after the patient's discharge the dosage of predisone was decreased to 30 mg. daily. She had occasional giddiness without loss of consciousness. Subsequently, on three occasions when the dosage of prednisone was decreased, she experienced dizziness and syncope. On each occasion after an increase in the dosage of prednisone the patient became asymptomatic, although complete heart block persisted.

Comment.—Prednisone therapy was effective on numerous occasions in preventing Adams-Stokes attacks without any change in atrioventricular conduction. Complete heart block persisted and the ventricular rate was unchanged, but asystolic intervals were prevented. This effect was apparently related to the dosage of prednisone.

Comment

In these six patients with chronic heart block, the amelioration of symptoms after administration of prednisone was characterized by a variety of responses. There was restoration of normal atrioventricular conduction on the initial trial of prednisone therapy in five of the six patients. All of them had been receiving isoproterenol, ephedrine, and/or atropine without effect immediately prior to the institution of prednisone therapy. Within 8 to 36 hours after the onset of therapy there was electrocardiographic evidence of improvement of atrioventricular conduction. When there was complete heart block at the time of prednisone therapy a period of partial heart block preceded the conversion to normal conduction, which usually occurred within 48 hours. Paralleling the improvement as revealed by electrocardiogram there was a marked clinical benefit with diminution and subsequent cessation of Adams-Stokes seizures.

In one patient (case 3) normal atrioventricular conduction persisted for several months after the cessation of prednisone therapy, but when heart block subsequently recurred, prednisone in the same dosage was ineffective. In another patient (case 1) normal atrioventricular conduction lasted only 12 days after cessation of therapy, but whenever complete heart block recurred normal conduction was always restored after prednisone therapy. It is apparent that the effectiveness of prednisone therapy varies from patient to patient and in any single patient from time to time. Although a reversion to normal conduction often occurs with the initial trial, subsequent usage may be without effect.

One patient (case 5) clearly demonstrated a dosage dependence during prednisone therapy. Reversion to normal conduction was accomplished on several occasions when prednisone was given in a dosage of 60 mg. per day. When the dosage was decreased to 30 mg. daily heart block and Adams-Stokes seizures recurred. When the dosage was raised to the original level, normal conduction again was restored. Normal conduction could be maintained with 60 mg. of prednisone but not with lower doses. This effect could not be maintained permanently, however, and despite large doses of prednisone complete heart block recurred.

In two patients (cases 2 and 4), although normal atrioventricular conduction was restored with use of prednisone, partial heart block recurred while they were on therapy without a change in dosage. These patients did not have a recurrence of Adams-Stokes attacks, however, and were clinically improved.

One patient (case 6) exhibited a response to therapy with prednisone which was qualitatively different from responses in the preceding cases. Repeated Adams-Stokes seizures occurred while this patient was receiving atropine, ephedrine, and isoproterenol. Within 8 to 24 hours after starting therapy with prednisone the patient was asymptomatic in spite of the persistence of complete heart block. The ventricular rate remained slow, but there were no longer asystolic periods. Every attempt to decrease or discontinue use of prednisone was followed by a recurrence of Adams-Stokes attacks.

Relationship Between Steroid Therapy and Clinical Results.—It is necessary to consider, first, whether corticosteroid drugs are actually to be credited with the clinical results after their use and, second, the possible mechanisms by which these effects might have been accomplished. The variable and unpredictable course of Adams-Stokes attacks is a noteworthy obstacle to distinguishing between their spontaneous and drug-induced cessation. Nevertheless, both in the cases here reported and those in the literature, in view of the frequency, severity, and duration of the attacks prior to corticosteroid therapy, the speed with which they disappeared after the start of treatment is sufficiently impressive to suggest that the beneficial effect was due to the use of corticosteroids. Furthermore, the attacks tended to recur with discontinuation of the drug therapy or reduction below a critical dosage, whereas the attacks were prevented when the drug was again administered in adequate dosage.

In the case reported by Prinzmetal and Kennamer[4] reversion of complete heart block to sinus rhythm occurred within a few hours after administration of ACTH, and when heart block recurred it promptly disappeared after further ACTH therapy. In the case reported by Phelps and Lindsay[5] Adams-Stokes attacks of increasing frequency for about 12 hours were occurring every few minutes, but only one last attack occurred soon after cortisone was given, and the heart block disappeared sometime within the next nine hours. Despite this time relationship, the association of the heart block with acute myocardial infarction raises the possibility of spontaneous disappearance of the heart block with subsidence of the acute infarction. This possible objection does not apply to the other cases culled from the literature or to the cases here reported.

In one of the cases reported by Tung and associates[7] there had been 23 Adams-Stokes attacks in a period of 48 hours preceding corticotropin therapy. Not a single syncopal attack occurred after treatment was started with ACTH, and within 24 hours complete atrioventricular block was replaced by regular sinus rhythm. In the second of their cases there had been eight Adams-Stokes attacks in 48 hours prior to treatment, three brief seizures soon after completing an intravenous infusion of ACTH, and three more seizures 12 hours later, but none thereafter. But in these cases complete heart block persisted.

In one of the cases reported by Litchfield and others,[8] the patient had been suffering Adams-Stokes attacks from 1 to 40 times daily for many weeks, but the attacks ceased within a few hours after corticotropin therapy was begun. In another case the patient had been suffering such attacks for eight weeks, and within six hours after the beginning of corticotropin therapy the attacks ceased. Similarly, in the cases reported here, Adams-Stokes attacks promptly ceased, and in some cases the attacks recurred when the prednisone therapy was discontinued and were repeatedly eliminated when prednisone therapy was resumed. As a rule normal conduction was restored within 12 to 36 hours. It was difficult to avoid the conclusion that the cessation of attacks and improvement in atrioventricular conduction was related to the treatment with prednisone.

Mechanisms of Beneficial Effect of Steroids.—Any explanation for the mechanism of the beneficial action of the corticosteroid drugs in these cases must account both for the improvement in atrioventricular conduction and for the control of the Adams-Stokes attacks. When atrioventricular conduction is improved and the ventricles respond to the sinus pacemaker the prevention of the Adams-Stokes attacks is obviously due to restoration of normal conduction. But it is apparent that incomplete and complete heart block may occur without Adams-Stokes attacks, and in our patients as well as the others to whom we have referred, the Adams-Stokes attacks were often eliminated before normal conduction was restored, and in some cases even though incomplete or complete heart block persisted.

That corticosteroids may accelerate or improve atrioventricular conduction is indicated by studies of the P-R interval in patients with adrenal cortical hypofunction (Addison's disease) and those with adrenal cortical hyperfunction (Cushing's disease). Lown and associates[10] found that the mean P-R interval in patients with adrenal cortical hypofunction was longer than that of normal controls and that 20% of the former had first-degree heart block during their illness. In most of those who received cortisone therapy there was a significant shortening of the P-R interval. Conversely, patients with adrenal cortical hyperfunction had a mean P-R interval which was shorter than the mean of normal controls; in a high percentage of the former the P-R interval was 0.12 seconds or less. After adrenalectomy had been performed the P-R intervals lengthened. The effect on the P-R interval was attributed to the glucocorticoid and not to mineralocorticoid adrenal secretion, because desoxycorticosterone acetate therapy had no effect on the P-R interval and because addisonian crisis which is associated with electrolyte disturbance likewise did not affect the P-R interval.

The mechanism by which the corticosteroids may accelerate atrioventricular conduction is unknown. Although the corticosteroids may tend to produce slight potassium depletion and alkalosis and although alkalosis accelerates atrioventricular conduction[11] there is no evidence to support such a mechanism to account for improved conduction in heart block after corticosteroid therapy. Sympathetic stimulation accelerates atrioventricular conduction.[1] Although there is no direct evidence that treatment with corticosteroids may increase the responsiveness of the atrioventricular conduction system to sympathetic stimuli, it is of interest to note that there are observations indicating an increase in vascular sensitivity (vasoconstriction) to norepinephrine after the administration of corticonteroids.[12] The anti-inflammatory action has generally served as the rationale for the use of corticosteroids in patients with heart block. This was the basis of its use in patients with acute myocardial infarction and the explanation of its effectiveness. Similarly in the cases reported by Tung and co-workers[7] these drugs were used because of the assumption of persistent rheumatic inflammation in the conduction system. However such an explanation is difficult to invoke in the cases here reported.

It is noteworthy that after therapy with corticosteroids the attacks of Adams-Stokes syndrome often ceased before there was any apparent improvement in atrioventricular conduction and even when complete heart block persisted. This indicates that the arousal and stabilization of ventricular pacemakers is an independent action and may occur earlier than any effect on atrioventricular conduction. There is no basis for attributing this important effect on idioventricular pacemakers to any anti-inflammatory action of the corticosteroids.

This report of encouraging results after corticosteroid therapy in cases of heart block and Adams-Stokes syndrome should not be regarded as necessarily representative of the effectiveness of these drugs in a much larger all-inclusive series of consecutive cases of this disease. We know of two other patients not under our care in whom the use of prednisone alone, in apparently adequate dosage, was ineffective in causing either symptomatic or electrocardiographic improvement. Undoubtedly favorable results are more likely to be reported than unfavorable ones. Furthermore, it is apparent that patients who appear to respond favorably at one stage of the disease may later become refractory to the same treatment. Similar variability of response has been noted with the other accepted and generally used methods of therapy.

In the six cases reported here the favorable response from administration of prednisone occurred after therapy with the other drugs had failed. The seriousness of the disease, the ready availability and simplicity of administration of corticosteroids, and the uncertainty of response of other therapies justify the prompt use of the corticosteroids at the onset of attacks of Adams-Stokes syndrome with heart block. Sympathomimetic drugs and artificial pacemakers, which usually cannot be used as promptly, can be used in conjunction with corticosteroids if the latter are ineffective.

Summary

Prednisone therapy was effective in abolishing Adams-Stokes attacks in six patients. In five of these atrioventricular conduction was improved or restored to normal. The frequency and duration of the seizures prior to treatment and the speed with which they were controlled after treatment suggest that the prednisone therapy was responsible for the beneficial effects. The Adams-Stokes seizures were abolished in some patients even when heart block persisted, suggesting that prednisone arouses and stabilizes idioventricular pacemakers as well as improves atrioventricular conduction. The use of adrenal glucocorticoids appears warranted in view of their immediate availability and simplicity of administration. Sympathomimetic drugs and an artificial pacemaker can be used simultaneously, if available, or added later if therapy with corticosteroids is ineffective.

1125 Fifth Ave. (28) (Dr. Friedberg).

Dr. Harry Jaffe supplied information on the patient in case 3, Dr. Arthur Grishman in case 4, and Dr. Howard Moscovitz in case 6.

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CLINICAL NOTES

ARTIFICIAL EMBOLIZATION OF CEREBRAL ARTERIES

REPORT OF USE IN A CASE OF ARTERIOVENOUS MALFORMATION

Alfred J. Luessenhop, M.D.
and
William T. Spence, M.D., Washington, D. C.

It has been the theoretical and technical consideration of one of us (A. J. L.) that certain large arteriovenous malformations of the brain can be treated by artificial embolization. The major feeding arteries are greatly enlarged compared to the arteries to the surrounding brain.[1] Because of the reduced peripheral resistance there is a far greater flow of blood to the malformation than to the surrounding brain.[2] The main arterial feeders arborize into considerably smaller, "arteriole-like" vessels before entrance into the larger channels which constitute the bulk of the lesion.[3] Therefore, an embolus of predetermined size and configuration, introduced even far proximal to the malformation, will always find its way to it. By its size the embolus will be excluded from passage into the smaller branches to the brain and will ultimately come to rest at a site proximal to the malformation where normal and abnormal vessels are seen to be clearly separate (fig. 1).

Herewith is the first reported case of an arteriovenous malformation of the brain treated by embolization according to the above considerations.

Report of a Case

On Sept. 11, 1959, a 47-year-old woman, referred by Dr. Bruce Mallett, was admitted to the Georgetown University Hospital about four hours after the rapid onset of a severe generalized headache, drowsiness, and impairment of vocal expression.

Since early childhood she had had frequent episodes of syncope. For 15 years prior to admission she had had occasional episodes of transient numbness and weakness of the right arm and leg, a slight loss of skilled movements of her right fingers, and periods during which she had difficulty in finding "the right word."

Initial examination revealed the following pertinent findings. The blood pressure was 100/80 mm. Hg, with a pulse rate of 80 per minute. She was drowsy and in moderate distress because of a headache. She showed a mild expressive dysphasia, slight nuchal rigidity, and mild right hemiparesis, with greatest involvement of the face, wrist, and fingers. There was a soft, blowing systolic bruit over the left eye. There was no evidence of cortical sensory loss.

A lumbar puncture revealed an initial pressure of 300 mm. of cerebrospinal fluid which was dark pink and without evidence of xanthrochromia. A percutaneous carotid angiogram on the left side was made 10 hours after admission, and one was made on the right side two days later. As shown in fig. 2, the angiogram on the left side revealed a large arteriovenous malformation intimately involving the areas of motor, speech, and the lower portion of the motor strip. The angiogram of the right side showed filling of both anterior cerebral arteries, with virtually no contribution to the malformation. The middle cerebral trunk on the left side was increased in diameter to about 5 mm. up to its point of division. More distally, there were many large trunks but precise measurements could not be made.

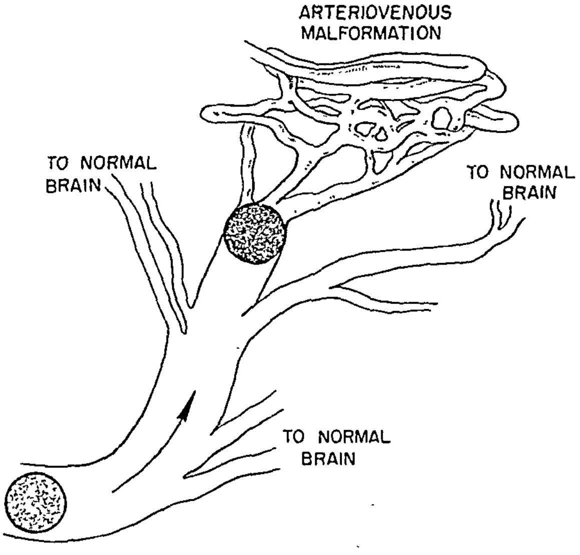

Fig. 1.—Embolus in main arterial channel, excluded from smaller branches to normal brain and forced to arrest at point proximal to malformation.

After eight hours of hospitalization the patient's headache subsided, but her expressive dysphasia in-

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From the Department of Surgery (Neurosurgery), Georgetown University Medical School, Washington, D. C.

creased, causing her to omit or alter at least one word per sentence. The paresis of her right hand, fingers, and face improved somewhat.

Operation was performed on Sept. 18, 1959, seven days after admission. With the patient under local anesthesia the left common carotid bifurcation was exposed. Four spherical emboli, made of methyl methacrylate,[4] were introduced at intervals of about 15 minutes. They measured successively about 2.5, 3.0, 4.0, and 4.2 mm. in maximum diameter. After introduction of each embolus, strength of the right arm and speech were tested and x-rays were taken to determine the site of arrest. Immediately after introduction of the fourth embolus the patient became drowsy and showed increasing weakness of the right hand but no alteration of speech. The angiogram made shortly thereafter is shown in fig. 3. The malformation was reduced to a slight stain, and for the first time normal filling of the anterior and middle cerebral arteries was evident. The emboli, identifiable by metallic fragments within the plastic coating, had come to arrest at the beginning of the malformation.

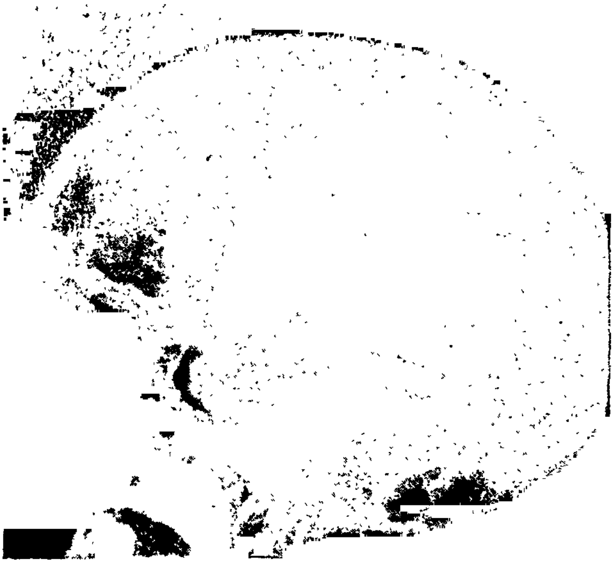

Fig. 2.—Lateral view of preoperative arteriogram, showing malformation.

The weakness of her right hand progressed over the next 14 hours until there was but feeble extension and flexion of the wrist and fingers. Thereafter the strength rapidly returned. Seven weeks after surgery she was able to write legibly with her right hand. At no time during her postoperative course was there any recurrence of her dysphasia or loss of cortical sensory function.

Roentgenograms of the skull taken five days after surgery was performed showed that the fourth embolus, represented by the large round fragment in fig. 3, had moved to a position closer to the malformation. This embolus, being larger than the others, had temporarily lodged too far proximal to the malformation and had thereby caused her transient neurological defect. The follow-up angiogram of the left carotid artery, made 26 days afte surgery, is shown in fig. 4. There is excellent fillin of the normal arteries and only a remnant of th malformation persists.

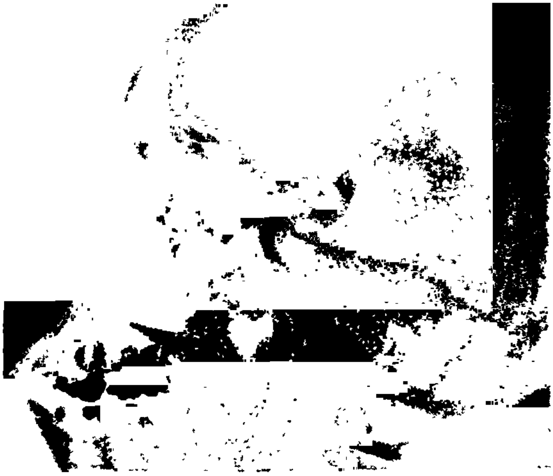

Fig. 3.—Immediate postoperative arteriogram, showin nearly complete obliteration of malformation and filling normal arteries.

Comment

Because this initial case was, to a large degre a trial of the theoretical considerations describe above, the emboli were made from material no likely to promote thrombosis. With further confirmation of the applicability of this method this safeguard need not be adhered to.

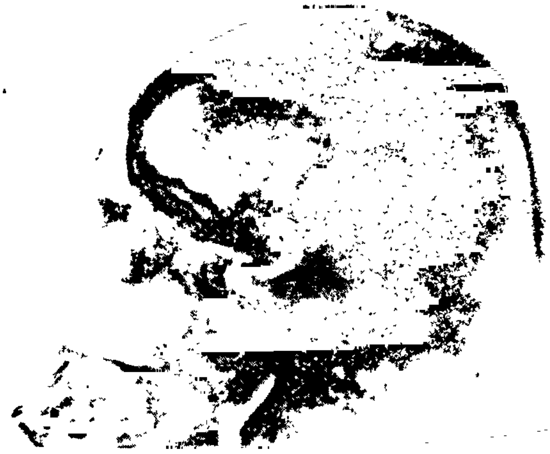

Fig. 4.—Arteriogram made 26 days after surgery; remnant of malformation persists.

Most large arteriovenous malformations are supplied primarily or solely by the middle cerebral artery.[1] This artery, being the natural continuation of the internal carotid, forms the route the emboli will naturally seek. However, with large malforma-

tions situated in the middle of the hemisphere and generously supplied by both the middle and anterior cerebral systems, prior embolization of the middle cerebral contribution will leave direct intracranial occlusion of the anterior cerebral feeders to effect a satisfactory result. Important cortical areas over the surface of the hemisphere will thereby remain undisturbed.

If the emboli can be retrieved by attachment of sutures or wire, an adaptation of this technique for the treatment of saccular aneurysms is possible. If the distance the embolus can ascend in the internal carotid artery is limited, it can be held in a position to occlude temporarily the intravascular orifice of the aneurysm. After thrombosis has occurred, recovery of the embolus is effected.

Summary

Theoretical considerations suggest that the differential in blood flow between an arteriovenous malformation and the surrounding brain, plus the differential in size among the arteries directly feeding the malformation, the branches to the brain, and the small arteries at the beginning of the malformation, will always lead an embolus of proper size to a site of arrest at the beginning of the malformation. A patient with large, inoperable malformation was satisfactorily treated by embolization.

The methyl methacrylate emboli used in this study are available from the L. D. Caulk Company, Milford, Del.

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PHOTOSENSITIVITY DUE TO TETRACYCLINE DERIVATIVE

William E. Morris, M.D., Corpus Christi, Texas

Dermatological manifestations have been reported from the use of many drugs, particularly antibiotics. With the widespread use of antibiotics, particularly the tetracycline derivatives, it is likely that photosensitivity will be found in the ordinary practice of medicine, particularly when warmer weather comes and more persons are exposed to sunlight. A single case of a severe reaction to demethylchlortetracycline hydrochloride was noted in September, 1959.

Report of a Case

A 30-year-old woman was suffering from a generalized ache, a sore throat, and a respiratory infection. She had a slightly elevated temperature and pulse rate; otherwise, physical findings were normal. On Sept. 1 she was put on therapy with demethylchlortetracycline (Declomycin) hydrochloride, 150 mg. four times daily, for four days. On Sept. 5 the patient went surf fishing and was exposed to sunlight over the arms, hands, neck, and face. Within 30 to 40 minutes she began to develop a severe tingling of the tips of the ears and the backs of the hands. She thought that she might be getting too much sun and immediately put on a shirt, but within another 30 minutes she was most uncomfortable and discontinued the fishing.

By the evening she was quite red over the dorsal surfaces of the hands and the tops of the ears, and a butterfly distribution of redness was noted over both cheeks. On Sept. 6 she had an extreme edema of the dorsal surfaces of the hands, across the bridge of the nose, over the cheeks, and over the ears, but none on the shoulders. She had ordinary sunburn on her shoulders but no edema or pain. At this time laboratory indexes showed a circulating eosinophil count of 2,331 per cubic millimeter. She was given ACTH in reducing doses and chlorprophenpyridamine (Chlor-Trimeton) by mouth, to which she began to respond in about 24 hours. On Sept. 18 she had 33 circulating eosinophils per cubic millimeter and an otherwise perfectly normal hemogram.

After the patient's condition had cleared completely, we decided to attempt to reproduce this situation and evaluated her condition Oct. 13; her circulating eosinophil count was 251 per cubic millimeter, with normal white and differential blood cell counts. She was given one capsule only of demethylchlortetracycline, 150 mg., on Oct. 31, without any subsequent symptoms. On Nov. 1 the patient began taking one capsule four times a day, which she took for four days. The next blood cell count showed an eosinophil count of 155 per cubic millimeter, with a platelet count of 160,000 per cubic millimeter and a normal hemogram. She was exposed to sunlight at noon on Nov. 4 and, within 20 minutes, she developed a typical erythema over the ears and the dorsal surfaces of the hands; the circulating eosinophil count had risen to 255 per cubic millimeter and the number of platelets had risen to 208,000 per cubic millimeter. She was

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From the Thomas-Spann Clinic.

immediately given diphenhydramine (Benadryl) hydrochloride by injection and by mouth and the condition cleared in four hours.

It is my purpose to exhibit a photosensitive rather than a phototoxic reaction to the offending antibiotic. I believe that, had the patient been left longer in the sunlight on Nov. 4, her condition might have progressed to more serious results; therefore the patient was not exposed to the full hazard of this situation. Demethylchlortetracycline has been used on 56 other patients without adverse reactions.

Summary

In a patient with photosensitivity to a new antibiotic, demethylchlortetracycline (Declomycin) hydrochloride, a considerable rise in the number of circulating eosinophils occurred after exposure to sunlight and a significant elevation in the count of circulating eosinophils after moderate exposure to sunlight after four days of treatment with this drug. Administration of antihistamines and steroids may be useful in the control of this condition.

1546 S. Brownlee St.

LIGHT SENSITIVITY DUE TO DEMETHYLCHLORTETRACYCLINE

REPORT OF FOUR CASES

Mortimer S. Falk, M.D., Reno, Nev.

Demethylchlortetracycline (Declomycin) is a recently introduced, broad-spectrum antibiotic produced by a mutant strain of Streptomyces aureofaciens. It is chemically closely related to the other known tetracyclines. Recent studies indicate that it may have an advantage over other tetracyclines, because comparable orally given doses produce greater and more prolonged serum activity against certain test organisms (Streptococcus 98, Staphylococcus 209P, and Bacillus cereus).[1] It is possible, therefore, that smaller and more widely spaced doses of demethylchlortetracycline may be at least comparable in clinical antibacterial activity to larger and more closely spaced doses of other tetracyclines.

In view of the relative effectiveness of the tetracyclines in controlling some cases of cystic and pustular acne, it was decided to use demethylchlortetracycline in a series of patients with this and other pyogenic dermatoses. The antibiotic was obtained in gelatin capsules containing 150 mg. (the unit dosage for the other tetracyclines is usually 250 mg.). It was given to 27 ambulant office patients in doses varying from 150 to 900 mg. per day for periods of from 3 to 128 days. Those who took the antibiotic for prolonged periods were on relatively small maintenance doses (150-300 mg.) during most of this period.

It is not the primary purpose of this paper to report the clinical results observed from use of demethylchlortetracycline. Moreover, the course of acne is such that the results of drug therapy, reported in exact quantitative statistics, are disputable. In general, however, the results were classified as follows: excellent six, good nine, fair (some improvement) eight, and poor four.

Four patients in this series experienced photosensitivity while taking the antibiotic. The reactions were manifested by erythema and edema of exposed portions of the skin. None were taking other medicaments concurrently. These reactions are cited in the following case histories.

Report of Cases

Case 1.—A 15-year-old, medium-complexioned high-school girl had moderately severe papulopustular acne of about two years' duration. On Sept. 10, 1959, she was given 24 demethylchlortetracycline capsules to be taken in a dosage of 300 mg. twice daily. When she was seen again, on Sept. 18, there was a pronounced erythema over the areas that had been exposed to sunlight, i. e., the face, neck, dorsal surfaces of the hands, lower legs, and dorsal surfaces of the feet. There were sharp lines of demarcation at the wrists, lower edge of the neck, and at the edge of her shoes. There was also edema and tenderness of the hands and feet. She was afebrile and had no complaints other than discomfort in the areas with solar erythema. She stated that she had not experienced prolonged exposure to the sun at any time during the week. As usual she had walked to and from school. The edema subsided in about one week, but the erythema persisted for one month after cessation of therapy with demethylchlortetracycline. It was followed by increased pigmentation of the involved areas.

Case 2.—A 25-year-old white male rancher had a grouped papular and folliculopustular eruption for at least five months, which involved the periorbital areas, the bridge of the nose, and the perioral region. The clinical and histological diagnosis was lupus miliaris disseminatus faciei, although results of the tuberculin test were negative. Treatment with demethylchlortetracycline was started on Sept. 16, 1959, with a dosage of 300 mg. twice daily. When he was seen on Sept. 29, he had taken 40 capsules (6 Gm.). There was a marked reddening of the face and neck, with sharp lines of demarcation in the nasolabial folds and submental region, indicative of a solar erythema. He was afebrile, and his only subjective complaint was a burning sensation in the involved areas. This man had worked outdoors for years, including the past summer, without ever having experienced a solar erythema of this intensity. Treatment with demethylchlortetracycline was discontinued, but it took about three weeks for the erythema to subside.

Case 3.—A 12-year-old girl, who had had a moderate papulopustular acne for about one year, was given 150 mg. of demethylchlortetracycline twice daily on Sept. 30, 1959. When she was seen on Oct. 7, after having taken 1.8 Gm. of the antibiotic, her face and neck were erythematous, and she complained of burning and itching. She had no other symptoms and was afebrile. The erythema subsided gradually over the next two and one-half weeks.

Case 4.—A 35-year-old woman had a mild papular acne, with a tendency toward premenstrual exacerbations. She also had tender subcutaneous nodules in the lower extremities which were compatible with a histological diagnosis of erythema induratum (Bazin's disease). On May 29 she was given demethylchlortetracycline, with instructions to take 150 mg. four times per day. From this date until June 15 she took 44 capsules (6.6 Gm.). On June 8, after having taken 4.2 Gm. of the antibiotic, no untoward reaction was apparent when she was seen in the office. The next week, after having taken an additional 2.4 Gm., she had a pruritic erythematovesicular eruption involving the nose and paranasal region, the chin, the dorsal surfaces of the hands and forearms, and sharply demarcated areas on the dorsal surfaces of the feet and toes corresponding only to portions of the skin which had been exposed to sunlight while she was wearing strap sandals and supportive elastic bandages which covered the middle and posterior part of her feet. She stated that she experienced a burning sensation in the involved areas after she had worked in her garden for about one-half hour during the previous week. Within the next few hours and the next day the areas became more erythematous and vesicles appeared on the hands and forearms. There were no other complaints. On June 26 the involved areas were still erythematous but the vesicles had subsided. By July 10 there was residual pigmentation on all the involved areas, and on Dec. 9 (six months later) pigmentation was still evident on the feet although the other areas appeared normal.

Comment

On the basis of this experience it appears that demethylchlortetracycline has photosensitizing properties. Four of 27 ambulatory patients developed sunburns on exposed areas while taking the antibiotic. None of the patients was taking another medicament which could be incriminated. Each of the four denied having experienced more prolonged exposure to sunlight than he or she ordinarily was accustomed to. It is of interest that one of the patients who exhibited this sensitivity to sunlight was a rancher (case 2) who had been outdoors daily throughout the previous summer and could therefore be expected to have built up a considerable tolerance to the erythema-producing portions of the ultraviolet rays. Nevertheless, in mid-September he developed a marked erythema which was sharply limited to exposed areas of the face and neck while taking demethylchlortetracycline. Three of the four patients who experienced reactions did so within a week, while one showed no evidence of photosensitivity until she had taken the antibiotic for more than two weeks. The daily dosage at the time the reactions occurred was 600 mg. for three of the patients but only 300 mg. for the fourth, the 12-year-old girl. Another interesting observation was the fact that the erythemas persisted longer than would ordinarily be expected, requiring from two and one-half to over four weeks to subside. One patient still had areas of pigmentation, corresponding to the reaction sites, on the dorsal surfaces of the feet, six months later.

Summary

Of 27 ambulatory patients 4, whose case histories are given, exhibited skin reactions indicative of photosensitivity while being treated with demethylchlortetracycline (Declomycin) for pustular acne and other pyogenic dermatoses.

505 S. Arlington Ave.

The demethylchlortetracycline used in this study was provided as Declomycin by Lederle Laboratories, Division of the American Cyanamid Co., Pearl River, N. Y.

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COMMITTEE ON MEDICOLEGAL PROBLEMS

Rh-Hr BLOOD TYPES—PRESENT STATUS

Alexander S. Wiener, M.D., Brooklyn, N. Y., Lester J. Unger, M.D., New York City
and
Milton S. Sacks, M.D., Baltimore

Recently a third report on the subject of medicolegal applications of blood-grouping tests was published by the Committee on Medicolegal Problems.[1] This report reviewed the available information about the human blood groups and their heredity, from the point of view of their applications in medicolegal problems of disputed parentage. It also summarized the facts concerning the fundamental problem of Rh-Hr nomenclature and on the basis of the available evidence recommended that "unless and until some other convention can be agreed upon, the original Rh-Hr notations be kept as the standard and sole nomenclature for preparing approved medicolegal reports on Rh-Hr types." Soon after this report and recommendation appeared, a protest was published by 33 well-known workers in the field of blood-grouping,[2] but their protest offered no evidence in support of their position nor did it attempt to refute the evidence on which the American Medical Association report was based. Accordingly, this protest cannot be taken seriously and, in fact, has been answered in detail.[3]

The wisdom of the recommendation regarding Rh-Hr nomenclature has been further demonstrated by recent observations on the Rh-Hr types. These findings cannot be fitted into the C-D-E triple-inheritance scheme of notations, though they fit readily into the Rh-Hr nomenclature and were indeed anticipated by the serologic concepts on which the Rh-Hr symbols are based. The Rh-Hr terminology takes into account the sharp distinction between agglutinogens and their serologic attributes (or blood factors), and a notable feature of it is the use of regular type for symbols representing agglutinogens, phenotypes, and blood group systems, while **boldface** type is used for symbols for blood factors and their corresponding antibodies and *italics* for symbols for genes and genotypes. Some workers have attempted, without success, to adapt these important conventions to the C-D-E symbols. As has been pointed out, however, those who use the C-D-E notations unwittingly accept as facts the erroneous implications of the symbols and thus are led into serious misconceptions, which, when applied to serologic or even medicolegal problems, may lead to an erroneous conclusion. This consideration was one of the chief reasons for the A. M. A. Committee's recommendation regarding Rh-Hr nomenclature, since in scientific matters accuracy always takes precedence over mere simplicity and convenience.

The purpose of the present report is to detail the advances in knowledge concerning the Rh-Hr types which have occurred since the publication of the report and particularly to discuss their medicolegal implications, including the problem of Rh-Hr terminology.

Blood Factors Associated with Factor $\mathbf{Rh_0}$

Blood Factors $\boldsymbol{Rh^A}$, $\boldsymbol{Rh^B}$, $\boldsymbol{Rh^C}$, $\boldsymbol{Rh^D}$.—It is well established that blood factor $\mathbf{Rh_0}$ holds a special central position in the Rh-Hr blood group system. For one thing, it is the most antigenic of the Rh-Hr blood factors, and the one to which the clinician must pay the most attention if he wishes to avoid hemolytic post-transfusion reactions and neurological sequelae in erythroblastotic babies, with their unpleasant medicolegal repercussions. Moreover, the $\mathbf{Rh_0}$ blood factor seems to be located in a special part of the surface of the Rh-Hr agglutinogen molecule, as shown by the fact that red cells can be coated or blocked with univalent $\mathbf{Rh_0}$ antibodies without interfering in their reactions with other Rh-Hr antibodies. Recent observations have further demonstrated the special nature of the $\mathbf{Rh_0}$ portion of the Rh agglutinogen molecule and have disclosed the existence of previously unrecognized serologic complexities.

The new Rh factors were discovered through the study of clinical problems in which $\mathbf{Rh_0}$-positive patients had become isosensitized and had antibodies in their serum seemingly identical in specificity with anti-$\mathbf{Rh_0}$. This seeming paradox was resolved by the demonstration that the antibodies in question failed to react with the patient's own $\mathbf{Rh_0}$-positive cells as well as with cells of certain other rare $\mathbf{Rh_0}$-positive persons. This proved that these antibodies, although *simulating* anti-$\mathbf{Rh_0}$, were actually different from anti-$\mathbf{Rh_0}$ in specificity. This made it necessary to assign special symbols to the antibodies. The first such case recognized was one involving a patient with $\mathbf{Rh_0}$ variant red blood cells; a similar case was reported in detail a few years later. One of the most striking cases was that reported by Wiener and Geiger[1] involving a woman with "standard" Rh$_o$-positive cells who was isosensitized to the Rh factor and had an erythroblastotic baby as a result. The authors showed that the antibody in this patient's serum was not only different from anti-Rh$_o$ but also different from the Rh antibody of patients in previously reported cases, as well as in a case reported about the same time by Rosenfield and co-workers.[5] Wiener and Geiger postulated and predicted that in "standard" Rh-positive cells, associated with blood factor Rh$_o$, there occur multiple other blood factors, Rh^A, Rh^B, Rh^C, etc., but that in certain rare Rh-positive persons one or more of these factors may be lacking, so that if an antibody is formed for the missing blood factor these Rh-positive persons will seem to be sensitized to the Rh$_o$ factor.

The serum from the first patient reported on is no longer available, and no symbol has been assigned to the antibodies of his case or those reported later or of the patient of Rosenfield and co-workers.[5] Wiener has assigned the symbol anti-Rh^A to the antibody of the patient studied by Wiener and Geiger and to the corresponding blood factor the symbol Rh^A. Unger and Wiener[6] then encountered another similar antibody in an Rh-positive patient who had a hemolytic post-transfusion reaction, and since it was shown to be different from anti-Rh^A, they assigned to it the symbol anti-Rh^B and to the corresponding blood factor the symbol Rh^B. A third such antibody was next found by Unger and Wiener[7] in the serum of a mother of a pair of erythroblastotic twins, to which they assigned the symbol anti-Rh^C. More recently a fourth such antibody, anti-Rh^D, was found by Sacks and co-workers.[8]

Table 1 summarizes the results of investigations carried out by Unger and others on the distribution of blood factors Rh^A, Rh^B, Rh^C, and Rh^D among Rh-positive caucasoid and negroid persons. As the table demonstrates, almost every person with Rh-positive blood has, in addition to blood factor Rh$_o$, the four blood factors Rh^A, Rh^B, Rh^C, and Rh^D. Persons with blood giving the reaction characteristic of standard Rh$_o$ and which lacks one or more of the associated factors (Rh^A, Rh^B, Rh^C, and Rh^D) are quite rare.

TABLE 1.—*Incidence of Persons with Rh-Positive Blood Lacking Blood Factors Rh^A, Rh^B, Rh^C, and Rh^D**

		Blood Factor Tested for							
		Rh^A		Rh^B		Rh^C		Rh^D	
Racial Group		Total	Negative	Total	Negative	Total	Negative	Total	Negative
Caucasoid	No.	1,293	0	1,104	2	730	2	542	0
	%		0		0.18		0.27		0
Negroid	No.	1,170	8	1,037	0	658	1	511	5
	%		0.68		0		0.15		0.98

* Data modified from those of Unger and others.[9]

Nomenclature.—Since typical "standard" Rh-positive blood has, in addition to factor Rh$_o$, all the associated factors, Rh^A, Rh^B, Rh^C, etc., there is no need to indicate this fact in the symbol. Only the rare atypical Rh-positive bloods which lack one or more of these associated blood factors require a special distinctive symbol. For this purpose it has become conventional to insert a small superscribed letter to indicate the missing blood factor or factors; for example, blood of type Rh$_1^{ab}$rh gives all the expected reactions of Rh$_1$rh except that it fails to react with anti-Rh^A and anti-Rh^B.

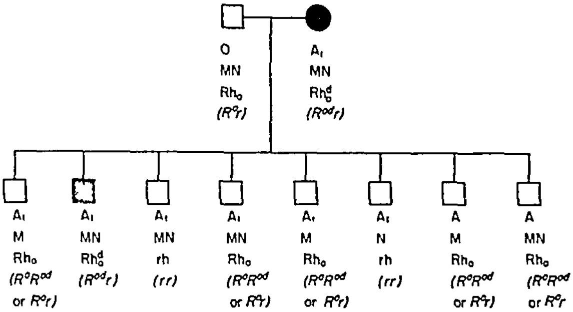

Fig. 1.—Family tree of patient, demonstrating hereditary transmission of agglutinogen Rh$_o^d$ by corresponding gene R^{od} (reprinted, with permission, from Sacks and others[8]).

Genetics.—It is reasonable to assume that the unusual varieties of Rh-positive blood which have been described are due to corresponding unusual Rh-Hr agglutinogens. For example, a person with blood of type Rh$_o^d$ presumably has in his blood an agglutinogen Rh$_o^d$ hereditarily transmitted by a corresponding allelic gene, R^{od}. That such is the case was proved by carrying out a family study, and the pedigree reported by Sacks and others[8] is shown in fig. 1. Since standard Rh genes, such as R^o, R^1, R^2, and R^z, each determine a corresponding agglutinogen, with all the blood factors Rh$_o$, Rh^A, Rh^B, Rh^C, and Rh^D inherited as a block, it is evident that the presence of agglutinogen Rh$_o^d$ can be detected only in persons of genotypes $R^{od}R^{od}$, $R^{od}r$, $R^{od}r'$ $R^{od}r''$, and $R^{od}r^y$ but not in persons of genotypes $R^{od}R^o$, $R^{od}R^1$, $R^{od}R^2$, etc., in whom the standard Rh agglutinogen will mask the presence of the atypical agglutinogen. This is illustrated by the pedigree shown in fig. 1.

An even more instructive pedigree was found earlier by Unger and Wiener[7] and is shown in fig. 2. In this case the unusual agglutinogen was designated $\mathfrak{R}h^c_2$, and the corresponding gene $\mathfrak{R}^{2c}$. The use of a Germanic capital $\mathfrak{R}$ was necessary to indicate that the Rh$_o$ factor in this case was not standard but a variant. In other respects, the pedigree shown is self-explanatory.

$\mathfrak{R}$h$_o$-Positive (Rh$_o$ Variant) Blood

Soon after the discovery of the Rh$_o$ factor, the existence of occasional bloods which reacted only weakly with the anti-Rh$_o$ agglutinating serum available at that time was observed. Because of the weak reaction of such bloods, they were said to have an intermediate Rh_0 factor. In tests on a large series of blood specimens from caucasoid and negroid persons, it was found that these unusual bloods were four to five times as frequent among negroid as among caucasoid persons. When the newer methods of testing by the conglutination, antiglobulin, and enzyme techniques became available, it was found that a graded series of bloods exist, ranging from typical Rh-positive to Rh-negative. The intermediate bloods are now known as Rh_0 variants ($\mathfrak{R}h$), the presence of an Rh_0 variant factor being indicated in the symbol by the use of a Germanic capital letter $\mathfrak{R}$. The original intermediate bloods first described would now probably be classified as "high-grade" Rh_0 variants. Modern techniques make possible the identification also of so-called medium and low-grade Rh_0 variant bloods. Such bloods fail to react at all with saline agglutinating anti-Rh_0 but react distinctly, by the antiglobulin technique, with univalent anti-Rh_0 serum. Thus, the symbol $\mathfrak{R}h$ includes a heterogeneous group of agglutinogens and blood types having in common the property of reacting atypically with anti-Rh_0 serum. Further light has been thrown on the nature of Rh_0 variants by the recent work on blood factors Rh^{A}, Rh^{B}, Rh^{C}, and Rh^{D}.

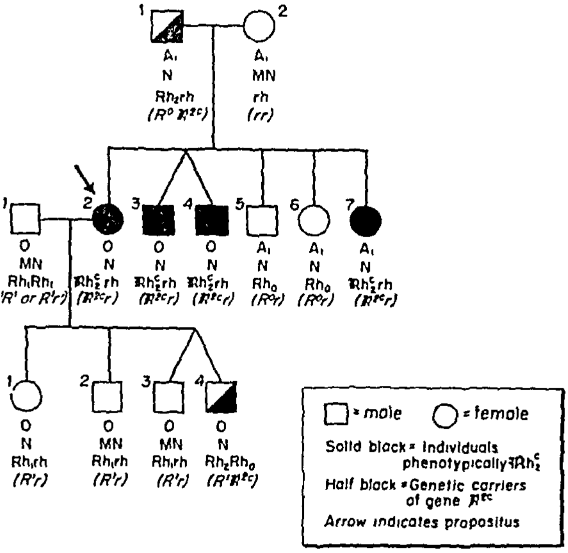

Fig. 2.—Family study, showing hereditary transmission of rare gene $\mathfrak{R}^{2c}$ (modified from Unger and Wiener[7]).

Tests carried out by Unger and others[9] *on a* series of more than 150 $\mathfrak{R}h$-positive bloods showed that most of these bloods lacked one or more of the blood factors Rh^{A}, Rh^{B}, and Rh^{C}; examples of all eight theoretical possibilities $\mathfrak{R}h$, $\mathfrak{R}h^{a}$, $\mathfrak{R}h^{b}$, $\mathfrak{R}h^{c}$, $\mathfrak{R}h^{ab}$, $\mathfrak{R}h^{ac}$, $\mathfrak{R}h^{bc}$, *and* $\mathfrak{R}h^{abc}$ *were encountered. More*over, when $\mathfrak{R}h$-positive blood had the factors Rh^{A}, Rh^{B}, *or* Rh^{C}, or any combination of these, these factors were almost always variants. By means of absorption experiments on pooled and selected anti-Rh_0 serum with Rh_0 variant blood specimens, *the existence of numerous serologic differences among such* Rh_0 *variant bloods* has been demonstrated. These findings become intelligible in the light of the findings of Unger and co-workers,[9] if it is assumed that the anti-Rh_0 serum used in the absorption experiments was polyvalent and contained, *in addition to* anti-Rh_0, anti-Rh^{A}, anti-Rh^{B}, and *anti-*Rh^{C}, *etc. and that the various absorbing* cells differed in their antigenic makeup. Thus, after absorption, different fractions of antibodies remained in the serums.

Medicolegal Implications

From the point of view of clinical medicine, Rh-positive persons who are sensitized to blood factors Rh^{A}, Rh^{B}, Rh^{C}, etc., should be treated like Rh-negative sensitized persons. Thus, if they require *blood transfusions, they may be given Rh-negative blood, and if such a female patient has an erythro*blastotic baby, Rh-negative blood should be used when the baby is treated by exchange transfusions. Failure to recognize the situation may lead to disaster, with medicolegal repercussions, *just as when sensitized Rh-negative patients are incorrectly trans*fused with Rh-positive blood. *Since the majority of* Rh_0-variant persons lack one or more of the factors Rh^{A}, Rh^{B}, Rh^{C}, etc., the problem is especially apt to arise with such patients. Therefore, this possibility *must be borne in mind, when patients with* Rh_0 *variant blood are treated, and for reasons presented* this problem will probably arise more frequently among negroid than among caucasoid persons.

From the point of view of disputed parentage, tests for Rh^{A}, Rh^{B}, Rh^{C}, Rh^{D}, etc., will yield useful results only in rare instances, because persons with Rh-positive (or $\mathfrak{R}h$-positive) bloods lacking one or more of these factors are rare. Paternity would be excluded in a mating such as rh × Rh_1rh, with a type Rh_1rh child, if it could be *shown that the Rh-positive parent* lacks one of the blood *factors* Rh^{A}, Rh^{B}, Rh^{C}, ... etc. but the blood factor in question is present in the blood of the child. On the other hand, in a mating such as Rh_0 × rh, with a type Rh_0 *child, if, for example, the Rh-positive parent and the child* both lack blood factor Rh^{D} (type Rh_0^{d}), this could be considered circumstantial evidence in favor of parentage, because blood type Rh_0^{d} is rare.

Blood Factors hr and rh_i

The recently discovered blood factors hr and rh_i have, on occasion, proved useful in resolving problems of disputed parentage. Blood factor *hr is a serologic attribute shared only by the agglutinogens rh and* Rh_0 *determined by the genes r and R'* respectively. On the other hand, according to the latest information, in caucasoid persons, factor rh_i is limited to the agglutinogens Rh_1 and rh' determined by the genes R^1 and r' respectively. Anti-rh_i, therefore, simulates anti-rh′ in specificity because of the low incidence of agglutinogens rh_y and Rh_z with which only anti-rh′ reacts (table 2).[9]

These two serologic reagents, anti-hr and anti-rh_i, are useful in resolving parentage disputes involving type $\mathrm{Rh}_z\mathrm{Rh}_0$ putative parents or children. For example, a type $\mathrm{Rh}_z\mathrm{Rh}_0$ person with a type rh or type Rh_0 child (or vice versa) would be excluded if he belonged to the common genotype R^1R^2 (or R^1r'' or R^2r') but not if he belonged to one of the rare genotypes R^zr or R^zR^0 or R^0r^y. Therefore, if the blood of such a putative father is hr-negative, he is excluded, but if it is hr-positive he is not. Similarly, if the blood of such a person is rh_i-positive, he is excluded, while if it is rh_i-negative he is not.[10]

From the points of view of serology, genetics, and nomenclature, blood factors hr and rh_i may be considered as additional associated blood factors of previously identified Rh-Hr agglutinogens, as in the case of factors Rh^A, Rh^B, Rh^C, Rh^D, etc. For example, at the present stage of knowledge agglutinogen rh is known to have a total of at least 4 blood factors: hr′, hr″, hr, and Hr_0; while agglutinogen Rh_1^w has a total of at least 10 blood factors: Rh_0, Rh^A, Rh^B, Rh^C, Rh^D, rh′, rh_i, rh^w, hr″, and Hr_0. (Anti-Hr_0 is presently defined as the antibody produced by sensitized persons homozygous for so-called double bar genes, i. e., persons of type $\bar{\bar{\mathrm{Rh}}}_0$, type $\bar{\bar{\mathrm{Rh}}}^w$, etc. "Double bar" Rh agglutinogens [e. g., type $\bar{\bar{\mathrm{Rh}}}_0$] are defined as those characterized by absence of the two pairs of contrasting blood factors rh′-hr′ and rh″-hr″. "Single bar" Rh agglutinogens [e. g., type $\bar{\mathrm{Rh}}_0$] are defined as those which lack only one pair of contrasting factors, namely rh″-hr″; recent work has shown that in chimpanzees, the Rh-Hr agglutinogen resembles the "single bar" human Rh agglutinogen.) The end is still not in sight, since as Wiener has predicted the number of blood factors characterizing an agglutinogen is limited only by one's energy and ingenuity in searching for and identifying antiserums of new specificities. At any rate, the blood factors which make up the serologic attributes of each agglutinogen are inherited as a block and transmitted by corresponding allelic genes, so that the individual blood factors do not represent separate agglutinogens inherited in three's or any other fixed number, as erroneously implied by the C-D-E notations.

Persons with blood of types $\bar{\bar{\mathrm{Rh}}}_0$ and $\bar{\bar{\mathrm{Rh}}}^w$ have been shown by family studies to be homozygous for the genes $\bar{\bar{R}}^0$ and $\bar{\bar{R}}^w$ respectively. These two genes are extremely rare, so that persons with blood of types $\bar{\bar{\mathrm{Rh}}}_0$ and $\bar{\bar{\mathrm{Rh}}}^w$ are generally the result of consanguineous marriages. The medicolegal importance of genes $\bar{\bar{R}}^0$ and $\bar{\bar{R}}^w$ is that, unless the expert takes their existence into account, he may misinterpret the results of blood tests and incorrectly exclude paternity or maternity. For example, a medicolegal case of disputed paternity, in which the mother belonged to type Rh_0 and the child to type $\mathrm{Rh}_2\mathrm{Rh}_2$, thus seemingly excluding maternity, was described in 1952. In this case, the mother was presumably genotype $\bar{R}^0r$, as shown by the weak reaction of her cells with anti-hr″ serum, and the child's genotype $R^2\bar{R}^0$. In an even more striking recent case, the putative father was found to be type $\mathrm{Rh}_1^w\mathrm{Rh}_1$, the mother type Rh_0, and the child type $\mathrm{Rh}_1^w\mathrm{Rh}_1$, so that the maternity of the child appeared to be excluded. Further tests showed that the mother's blood gave a "single-dose" reaction with *anti-hr′ and anti-hr″ serums*, while the child's blood cells gave a single-dose reaction with anti-hr″ serum and reacted much more weakly with anti-rh′ serum than the father's cells. Therefore the mother's phenotype was corrected to read $\bar{\bar{\mathrm{Rh}}}_0\mathrm{rh}$, and the child's $\mathrm{Rh}_1^w\bar{\bar{\mathrm{Rh}}}_0$, so that maternity was not excluded. In this case, considering the low frequency of gene R^{1w}, the findings instead provided circumstantial evidence that the accused man was the actual father of the child.

TABLE 2.—*The Eight "Standard" Rh Genes, Their Corresponding Agglutinogens, and the Major Blood Factors of Each Agglutinogen*

			Reactions of Three "Standard" Rh Serums			Reactions of Two Hr Serums		Reactions of Two "Special" Serums		
Genes	Agglutinogens	Frequency Among Caucasoid Persons in New York City, %	Anti-Rh_0	Anti-rh′	Anti-rh″	Anti hr′	Anti-hr″	Anti-rh_i	Anti-hr	Blood Factors Present
r	rh	38.0	—	—	—	+	+	—	+	hr′, hr″, and hr
r'	rh′	0.6	—	+	—	—	+	+	—	rh′, rh_i, and hr″
r''	rh″	0.5	—	—	+	+	—	—	—	rh″ and hr′
r^y	rh_y	0.01	—	+	+	—	—	—	—	rh′ and rh″
R^0	Rh_0	2.7	+	—	—	+	+	—	+	Rh_0, hr′, hr″, and hr
R^1	Rh_1	43.0	+	+	—	—	+	+	—	Rh_0, rh′, rh_i, and hr″
R^2	Rh_2	15.0	+	—	+	+	—	—	—	Rh_0, rh″, and hr′
R^z	Rh_z	0.2	+	+	+	—	—	—	—	Rh_0, rh′, and rh″

Rh-Hr Consultation Laboratories

The newer findings point up the need for additional consultation laboratories having available reagents of unusual specificities and panels of donors of rare Rh-Hr types, not only for clinical purposes but also for their research value. For example, there is need for laboratories to which blood specimens can be sent to resolve unusual clinical problems, notably cases of Rh-positive sensitized patients with Rh antibodies in their serums. It would also be of interest to have available persons of rare Rh-Hr types, such as rh'rh″, rh_yrh, $\text{rh}'^{w}\text{rh}$, Rh_1^{ab}, Rh_0^{a}, etc., whose blood is useful for testing Rh antiserums in order to determine their specificities.

Summary

Supplementing previous reports on the medicolegal applications of blood-grouping tests, the present report surveys developments of the past few years. New Rh-Hr factors Rh^A, Rh^B, Rh^C, Rh^D, etc., hr, and rh_i are discussed and their clinical and medicolegal importance explained.

64 Rutland Rd. (Dr. Wiener).

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PRELIMINARY COMMUNICATIONS

METHAMINODIAZEPOXIDE

Titus H. Harris, M.D., Galveston, Texas

A new drug, with a broad range of pharmacological activity, gives promise under current clinical testing of having diverse therapeutic applications. Methaminodiazepoxide (7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide hydrochloride), one of a new class of compounds, exerts three primary actions, namely, (1) tranquilization, (2) muscular relaxation, and (3) anticonvulsant effect. According to Randall[1] it is unlike other tranquilizers in that it calms laboratory animals without inducing sedation or motor inhibition. While possessing the tranquilizing properties of chlorpromazine and reserpine, it lacks their autonomic blocking effects. It is more active than meprobamate, chlorpromazine, and phenobarbital in antagonizing pentylenetetrazol (Metrazol)-induced convulsions; more potent than the first two in preventing electroshock convulsions, and different from phenobarbital in that it does not induce hypnosis. It blocks spinal reflexes at lower dosages than meprobamate, a property which accounts for its stronger muscle-relaxant effects.

Its unique action on vicious, agitated monkeys, dingo dogs, and other wild animals stimulated the first clinical trials with the drug. At a recent symposium (University of Texas Medical Branch Symposium on Newer Antidepressants and Other Psychotherapeutic Drugs; Their Use in Psychiatry and Other Branches of Medicine, Nov. 13 and 14, 1959), investigators in a number of medical specialties, including internal medicine, cited impressive results obtained from use of methaminodiazepoxide *in a variety of conditions and a freedom from side-*effects at therapeutic dosage levels. These investigations confirm my findings that the drug reduces anxiety and agitation but does not cloud consciousness or impair intellectual function. My experience with its use in all types of anxiety, convulsive disorders, tension states, obsessive-compulsive conditions, agitated depressions, and jitters in alcoholics

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Chairman and Professor, Department of Psychiatry and Neurology, University of Texas Medical Branch.

indicated that methaminodiazepoxide is one of the most interesting drugs of its type that has been developed. Of special interest is its apparent effectiveness in obsessive-compulsive neuroses, which have thus far defied chemotherapeutic management. It has been shown to have a margin of safety greater than meprobamate, and it approaches the activity of the phenothiazines, without their potential toxicity, in decreasing anxiety, mainly in neurotic patients. In certain patients the compound has a calming effect, while in others it has an elevating effect and increases drive; there are no extrapyramidal complications. A site and mode of action have not been delineated.

Methaminodiazepoxide has been subjected to extensive clinical study in general hospitals, where it was used in patients whose primary disorders were complicated by a psychoneurotic component. Breitner[1] reported successful results from its use, chiefly in patients with obsessional states. Kinross-Wright[1] found the drug to be most helpful in neurotic patients exhibiting anxiety and tension. Bowes[1] used it successfully in clinic outpatients with "long-standing anxiety and phobic reactions and in some obsessional states." Excellent results were also achieved in reactive depressive patients. Constant[1] observed that the drug shortened the course of electroconvulsive therapy (ECT) in private patients and made the agitated depressive patients more accessible to treatment with monoamine-oxidase inhibitors and psychotherapy. Sussex[1] reported success in the treatment of patients with "chronic mixed neurotic states with a neurasthenic, hypochondriacal, passive-dependent depressed symptom pattern."

Kaim[1] reported that methaminodiazepoxide demonstrated both tranquilizing and anticonvulsant properties in a group of epileptics with a long history of seizures. The frequency of seizures was reduced, and, in some instances, the electroencephalographic patterns were completely normalized. Favorable results with use of the drug have been reported in the management of alcoholics during the acute withdrawal phase. Thomas[1] noted a positive response in about 70% of ambulant patients with functional and psychophysiological disturbances that were referable chiefly to the gastrointestinal tract. Robinson[1] used the drug adjunctively in the treatment of dermatoses associated with emotional reactions, such as trichotillomania parasitophobia and neurotic excoriations, and in dermatoses which may precipitate anxiety states or depressions, i. e., severe acne with scarring, psoriasis, alopecia, and lupus erythematosus. Relief of emotional tension, control of anxiety states, and elimination of the need for bedtime sedation were observed after therapy with methaminodiazepoxide.

In human tolerance studies of the drug under controlled conditions, there was no evidence of cardiovascular disturbances and no significant changes were observed in hematocrit values, red and white blood cell counts, or kidney or liver function. The only important side-effects were drowsiness and ataxia. Drowsiness frequently subsided spontaneously after a day or two, and always with a slight decrease of the dose. Ataxia is a clinical sign of excessive dosage and disappears with smaller doses. Increased appetite and weight gain, which may be desirable effects in tense, anxious patients, have been reported.

The onset of action of methaminodiazepoxide is prompt, usually within one day, sometimes within a few hours. Evidence of habituation or postmedication depression has not been observed. Usually methaminodiazepoxide is administered orally, but it has been given in single intravenous doses as an aid to diagnosis in acutely agitated patients.

The methaminodiazepoxide used in this study was supplied as Librium by Hoffmann-La Roche, Inc., Nutley 10, N. J.

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BERYLLIUM POISONING.—The metal, beryllium, is of great importance in building and operating atomic reactors. It seems likely that metallurgists will succeed in making it ductile and workable, which will greatly extend its use as it is the lightest metal known. Our first toxic troubles from beryllium came from fluorescent lamp manufacture where a complex beryllium silicate was used as a phosphor lining for the fluorescent tubes. Acute poisonings occurred and soon a number of chronic poisonings, many of which were of long duration and fatal. All of them, acute and chronic, probably resulted from breathing beryllium compounds sometimes in concentrations ordinarily considered as "trace amounts." . . . The precautionary measures now being applied in the processing of beryllium are comparable in severity to those used in handling very toxic gases or radioactive materials. There are still poisonings from exposures of some years ago, but it is felt that control is at last becoming effective, while advances in the medical management of Be poisonings have been very great.—P. Drinker, Industrial Hygiene and Air Pollution, *The Royal Society for the Promotion of Health Journal*, July-August, 1959.

THE JOURNAL
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LINOLEIC ACID CONTENT OF FATS AND OILS

IT IS accepted generally that specific alteration in the diet will lower the concentration of cholesterol in the blood. The most effective results to date have been achieved by increasing consumption of polyunsaturated fatty acids, particularly linoleic acid. However, indefinitive and conflicting information has left much to the imagination of some food processors. Some of the largest vegetable oil processors in the United States have implied in advertisements that the cholesterol level can be lowered merely by adding polyunsaturated fatty acids to the diet. This selling campaign has created confusion among lay people, making it increasingly important that the physician clarify for his patients the conditions under which changes in the diet will be effective.

The patient should understand that if he increases his consumption of polyunsaturated fatty acids without reducing his intake of other fats, little is gained save for additional calories which could lead to obesity. A particular regimen will be effective only if polyunsaturated fatty acids are responsible for an appreciable percentage of the total fat calories. That is, they must replace rather than supplement some of the saturated fats and oils already in the diet.

The physician may find it difficult to evaluate the actual therapeutic value of various products sold by food processors. He may prescribe drugs with the knowledge that they are essentially as the manufacturer states them to be, but he cannot recommend food products with the same sense of security. They are not regulated as closely by the federal government and their claims must be interpreted with caution and understanding.

Many vegetable fats and oils contain appreciable amounts of the polyunsaturated fatty acids and if used properly will lower the blood cholesterol level. Some of these oils, like cottonseed and corn oil, are plentiful. Others, like peanut, safflower, and soy oil are available only in limited supplies. Sour cherry seed, watermelon seed, sesame seed, walnut, wheat germ, and sunflower seed oils are esoteric in origin and in limited supply.

Contrary to statements sometimes made, not all animal fats are low in the polyunsaturated fatty acid content nor are all vegetable oils high in this quality. The depot fat of chicken is an excellent source of linoleic acid. Coconut oil, a vegetable product, has an extremely low concentration of linoleic acid. Fish and marine oils are reputed to be uniformly rich in polyunsaturated fatty acids. The position of the marine oils is debatable, as these oils frequently contain fatty acids of the C_{20}, C_{22}, and C_{24} series. The influence of these longer length molecules has not been evaluated fully.

Claims for various hydrogenated vegetable oils must be assessed with the knowledge that the hydrogenation process converts polyunsaturated fatty acids into monounsaturated fatty acids or completely saturated compounds. Commercial hydrogenation solidifies liquid oils and increases their storage time without rancidity. The sequence of events, though controllable to some extent, usually is polyunsaturate → monounsaturate → saturate. A product may be derived from 100% cottonseed or corn oil, but when it is hydrogenated, it loses most or all of its polyunsaturated qualities. Heating vegetable oils to the usual cooking temperatures does not significantly impair their polyunsaturated quality. Vegetable oil is converted to solid margarine by one of two procedures. In one method, a solidifying agent such as a measured amount of a saturated or hydrogenated high melting fat is mixed with pure oil. The only resulting loss of polyunsaturated fatty acids is by dilution. In the other method, direct hydrogenation is used to raise the melting point. This process significantly reduces polyunsaturated fatty acid content.

Some manufacturers cite the "iodine number" of a fat or oil as evidence of the unsaturated fatty acid content of their product. This number is not a reliable indicator of therapeutic value because it measures monounsaturated and polyunsaturated fatty-acid content at the same time. A monounsaturated acid, like oleic, takes up two iodine atoms but does not affect the cholesterol concentration of the blood. A polyunsaturated acid, like linoleic, takes up four iodine atoms. In a product containing large amounts of oleic acid and small amounts of linoleic acid, the iodine number is nearly the same as it would be for a product containing little oleic acid and a modest amount of linoleic acid. Cottonseed oil has an iodine number of 110 and corn oil a number of 127; yet they each have about the same amount of linoleic acid.

At one time, some physicians advocated the "low fat, low cholesterol" type of diet as a means of lowering the cholesterol level of the blood. Though this recommendation reappears from time to time, it is now generally believed that dietary cholesterol, within the limits of the average mixed diet, plays little part in raising the cholesterol concentration in the blood. Total exclusion of certain animal products from the diet to achieve a low cholesterol intake rarely is justified. In fact, many cholesterol-containing foods are important sources of valuable protective nutrients.

Low-fat diets will not reduce the concentration of circulating cholesterol and lipoproteins as effectively as will diets containing an adequate percentage of polyunsaturated fatty acids. Weight-reduction regimens are basically low in fat, and if a lowered cholesterol level is necessary, planning must be done to maintain the proper ratio of saturated to unsaturated fats. When caloric requirements are above 3,000 a day, the diet still can include many food items containing saturated fats, but caloric intakes under 2,500 require specialized attention. The invisible fat inherent in the American high meat diet is largely of the saturated type and a most meticulous replacement for visible fats is necessary. When chicken or fish is the source of invisible fat, greater latitude can be had. Pork products, which contain about 10% linoleic acid, allow for some latitude. Many nuts and grain products contain appreciable amounts of linoleic acid (except coconut, cashew, and macadamia) and may be included in the diet for variety. Because of widespread misinformation in this field, the physician must carefully evaluate new developments so that he can effectively advise his patients about dietary changes with the same knowledge and confidence he draws on when prescribing drugs.

Herbert Pollack, M.D.
Assistant Professor of Clinical Medicine
Postgraduate Medical School
New York University.
New York.

CYTOLOGICAL SCREENING TECHNIQUES

The cervix is the second commonest site for cancer in women in the United States; in women of some other countries it is the commonest site. However, if treated adequately, cancer of the cervix has the best prognosis of all major forms of malignancy. The most important single factor influencing prognosis is the extent of the disease. The combination of cytological study of vaginal fluid and biopsy of the cervix results in a nearly perfect diagnostic score. This procedure could reduce significantly cancer of the cervix as a cause of death, if it were applied regularly to all women, or at least to all past 35 years of age.[1] The experience of the Strang Cancer Prevention Clinic at Memorial Hospital in New York City, together with studies being completed on 108,000 women in Memphis, Tenn., under the auspices of the United States Public Health Service, substantiates this assumption. The screening of presumably healthy women by the Papanicolaou method of exfoliative cytology is practical and leads to the discovery of many curable cancers of the cervix.

The opinion has been voiced that qualified cytologists are in short supply and that it is grossly impractical to plan for the periodic cytological study of a majority of women 35 years of age and older. However, technical cytologists can be trained to perform a portion of the job that is expected now of certified pathologists. The statement of Shields Warren, made a decade ago, remains: "It is a special advantage of the method that a large part of the diagnostic work may be done by one who has been trained in the technique. No broad background in pathology and cytology is required to recognize many types of cells. Competence in diagnosis depends mainly on experience with vaginal smears."

In spite of this evidence too few women throughout the nation undergo regular cytological examination. This deficiency is related in part to the lack of cytological services for physicians who are not affiliated with relatively large hospitals. General practitioners whose offices should be the front line of cancer detection often hesitate to make use of cytology centers geographically remote.

The U. S. Public Health Service reports in publication 671, January, 1959, that "a mass cytologic screening for uterine cancer is equally effective whether carried out entirely by private physicians on a mail order basis or by large, public, metropolitan clinics." This finding is based on a 10-year study by William Stoval and Paul Calabresi of the Wisconsin State Laboratory of Hygiene at Madison, Wis., who completed an effective case-finding program, carried out by private physicians, in which specimens were mailed to a central screening laboratory. In this screening survey 705 of the 805 malignancies present in 65,163 women were discovered. It is thus possible for most physicians, no matter how remote their practice may be from a medical center, to offer their patients the benefit of periodic vaginal cytological examinations. Furthermore, it may not be many months before an automatic cytoanalyzer is perfected which will expand

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the scope of such a program. If these technical developments are to be paralleled by an intensive educational program, then the hope expressed by Cameron[2] that periodic cytological examination "should make death from cancer of the cervix a rare event instead of the first cause of death from cancer among women" will indeed be realized.

Whatever the techniques used for preliminary screening, the basic concept in the diagnosis of disease and the particular medium must not be overlooked, i. e., that the procedure discussed is a screening technique and nothing more. The pathologist and the physician are not released from any ultimate responsibility. The pathologist, with his trained eye and judgment, should always counsel the physician for subsequent steps of professional action when smears show positive or doubtful results.

THE LAST OF THE HOPKINS FOUR

The publication of the biography of Dr. Howard C. Kelly[1] completes the tetralogy of the illustrious men of Johns Hopkins University School of Medicine who built an institution with enviable accomplishments. Kelly was the last of the four to join the distinguished group. His biography has been the last to be published. Harvey Cushing[2] was awarded the Pulitzer prize in biography in 1926 for his two-volume recounting of the "Life of Sir William Osler." The story of William H. Welch, the pathologist, who was largely responsible for the design of the Hopkins concept, was told by the Flexners[3] in 1941. William Stewart Halsted, surgeon and the most controversial member of the quartet, owes his biography to a one-time pupil and academic associate, Samuel J. Crowe.[4] And now, Audrey W. Davis, friend and confidante of Howard C. Kelly for two decades, has prepared the first full-length biography of this brilliant general surgeon and gynecologist who was as devoted to Christianity as he was dedicated to his profession.

Kelly was born in 1858 in Camden, N. J., and lived his 85 years in the environs of Philadelphia and Baltimore. He inherited a deep spiritual insight from his maternal grandfather, a clergyman, and a lifelong interest in the natural sciences from his mother. His father's contributions were spiritual and material—the latter because of his interest in the sugar industry. The University of Pennsylvania claimed Kelly as an undergraduate as well as a medical student. Summers afforded him leisure time for the pursuit of biology and other phases of natural science. A great many hours and days were spent in the out-of-doors. One summer was spent on a ranch in Elbert County in the Colorado Rockies. A physician who attended the construction crew charged with drilling a tunnel through the Continental Divide was numbered among hi professional friends. The doctor, George H. Simmons, was appointed editor of THE JOURNAL a decade later.

Fame and responsibility came to Howard C Kelly at an early age. He was scarcely 31 years o age when he was invited by President Gilman o Johns Hopkins University to head the departmen of obstetrics and gynecology in the medical schoo Simultaneously he was appointed chief of the clinical departments at the Johns Hopkins Universit Hospital. Until he relinquished his academic pos at the age of 60 years, his professional days wer prolific in writing, stimulating in developing youn men, bountiful in honors, and professionally frui ful as a skilled disciple of Asclepius. He shared common belief that a gynecologist should be qualified abdominal surgeon first. This is born out by the publication in 1905 of his monograp on the vermiform appendix. This followed only few years his two-volume treatise on operativ gynecology. Max Broedel, the medical artist o renown who had been invited to Johns Hopkin from Germany in 1894, illustrated these works.

The Flexner report on medical education appeared in the midst of Kelly's brilliant career. Th strong recommendation in support of full-tim clinical departments provoked much discussion a Hopkins as it did in many medical schools. Osle as well as Kelly was opposed to the full-tim system, although it is debatable whether the opportunity to collect consultation fees from privat patients interfered seriously with the scientifi contributions of either teacher. Kelly relinquishe his academic post at Hopkins in 1919 and concentrated his professional activities in private practice. His ancillary activities included philanthrop —medical, religious, and academic—motivated b a capacity to raise money from friends and patient for each of these three areas when the need arose

Kelly's interest in the out-of-doors continue until late in life. At the age of 71 years he expresse keen disappointment in being thwarted from goin down the Colorado River by boat, following the pattern of Powell and Dellenbaugh, a half centur earlier. The Colorado River is navigable over th treacherous runs late in the spring for a few week only. At the time selected for Kelly's party the rive was swollen beyond a dangerous level, and th trip was abandoned.

Many honors came to the "Prince of Gynecology." Probably the most distinguished was the degree of Doctor of Laws *honoris causa*, given b Johns Hopkins. He died in his 85th year, precedin by only a few hours the death of Mrs. Kelly.

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ORGANIZATION SECTION

STATEMENT TO HOUSE OF REPRESENTATIVES COMMITTEE ON VETERANS' AFFAIRS ON H. R. 7966

January 28, 1960

Honorable Olin E. Teague, Chairman
Committee on Veterans' Affairs
House of Representatives
Washington 25, D. C.

Dear Mr. Chairman:

I should like to take this opportunity on behalf of the American Medical Association respectfully to submit for your consideration our views on H. R. 7966, 86th Congress, a bill which we understand is now pending before your Committee.

This bill would amend the definition of "medical services" in Section 601(6) of Title 38, United States Code to include the services of optometrists. This is general terminology and might be interpreted to include the diagnosis of eye diseases, the consideration of problems dealing with the prevention of blindness and the conservation or restoration of vision. Inasmuch as these activities constitute the practice of medicine, it is our considered opinion that they should be performed exclusively by qualified doctors of medicine.

We believe, as I am sure the Committee does, that veterans with service-connected conditions, of all people, are entitled to the highest quality of medical care. We do not, however, believe that this objective can be realized if the providing of eye care by optometrists is authorized by Congress.

The granting to optometrists of the right to perform eye examinations for veterans may result in a failure to administer necessary sight-saving medical treatment and rehabilitative care. Unfortunately, in too many cases proper treatment has been delayed or possible rehabilitation or cure denied because of a diagnosis rendered by others than qualified medical practitioners. On the other hand, the exercise of medical skills by qualified physicians insures the early detection and successful treatment of the organic and systemic causes of blindness.

For the reasons stated above the American Medical Association is opposed to the enactment of this legislation.

It is my hope that this statement can be made a part of the record of your hearings. If we can be of service to your Committee in any way, you may be assured of our willingness to cooperate.

Very truly yours,
F. J. L. Blasingame, M.D.
Executive Vice-President.

STATEMENT TO HOUSE OF REPRESENTATIVES COMMITTEE ON VETERANS' AFFAIRS ON H. R. 2412

January 25, 1960

Honorable Olin E. Teague, Chairman
Committee on Veterans' Affairs
U. S. House of Representatives
Washington 25, D. C.

Dear Mr. Chairman:

The purpose of this letter is to submit for the consideration of the Committee on Veterans' Affairs the official position of the American Medical Association on H. R. 2412, 86th Congress, which we understand will be the subject of hearings by your Committee today. H. R. 2412 would grant veterans of the Spanish-American War, the Philippine Insurrection and the Boxer Rebellion unlimited eligibility for hospital care from the Veterans' Administration for any disability by establishing the presumption that any disability of such a veteran would be held to be a service-connected disability incurred or aggravated in a period of war.

The American Medical Association is, and always has been, in complete agreement that the Federal Government has a duty to care for any person who has a physical or mental disease or disability caused or aggravated by military service. We believe, however, that the provision of medical care and hospitalization by the Federal Government for veterans with non-service-connected disabilities is unsound. This position was reaffirmed by the House of Delegates of the American Medical Association as recently as December, 1959, when it stated that federal responsibility for the provision of hospitalization and medical care should be limited to veterans with service-connected diseases and disabilities. It is the belief of the Association that the care of veterans with non-service-connected conditions should be the responsibility of the individual or his family or, if he is indigent, of the community or state government.

Therefore, we are opposed to H. R. 2412 which would expand the provision of medical care and hospitalization by the Federal Government for veterans with non-service-connected conditions. This bill would be particularly unacceptable since it would arbitrarily categorize the disabilities of this group of veterans as service connected without the requirement of proof or in spite of convincing evidence to the contrary. This device would negate completely the statutory and regulatory safeguards that do exist in the wholesale provision of medical and hospital care in non-service-connected cases.

Further, we oppose this legislation because it would constitute a precedent which in later years could lead to the Federal Government providing medical care for all veterans regardless of the cause of their illness or injury. The provision of such care for Spanish-American War veterans and other beneficiaries under this legislation would soon lead to pressure to provide the same care for veterans of World War I, World War II, and the Korean conflict.

We will appreciate your arranging to have this letter made a part of the record of your hearings.

Sincerely yours,
F. J. L. Blasingame, M.D.
Executive Vice-president.

STATEMENT TO SENATE INTERSTATE AND FOREIGN COMMERCE COMMITTEE ON S. 1283

January 27, 1960

Senator Warren G. Magnuson, Chairman
Interstate and Foreign Commerce Committee
United States Senate
Washington 25, D. C.

Dear Mr. Chairman:

On August 13, 1959, the American Medical Association submitted a statement outlining its position on S. 1283, 86th Congress, for inclusion in the record of the hearings on this bill. The statement recommended the following modifications:

1. Extension of the scope of the bill to include all hazardous substances "distributed as packaged chemicals for non-manufacturing purposes."
2. Application of the proposal to hazardous substances intended for export to any foreign country.
3. Inclusion of warning symbols for extremely dangerous substances.

Later testimony presented to your Committee raised questions concerning two important provisions of the bill. For this reason, we would like to supplement our original statement.

A recommendation was made by Doctor Emil Klarman, representing the Chemical Specialties Manufacturers Association, which in our opinion if accepted would seriously dilute the effectiveness of the proposed legislation. He advocated the omission of toxicologic tests in determing the necessity for the signal word "danger" and recommended that the term be applied only to very toxic substances which would also be labelled "poison." The reasons given for this proposed modification are that the present provisions would require "an enormous amount of laboratory work" and, in the words of a subsequent witness (Mr. Nicholas Walker), "would tax laboratory facilities. . . ."

The American Medical Association does not believe that these recommendations are sound. Objection to toxicity standards, because they overta testing facilities, is a recurring but unfounded fear This fear has been expressed during the consideration of every legislative improvement in the regulation of chemicals from the Federal Caustic Poiso Act of 1927 to the current legislative debate ove the regulations of chemical additives to food Admittedly, the provisions of S. 1283 would requir more toxicity testing than has heretofore been undertaken for these products. However, improve protection for consumers against bodily inju necessitates and justifies the additional work. I addition, experience with older laws indicates th the economics of the problem will insure faciliti and personnel to meet the demand. We strong recommend maintaining the toxicity standards f "danger" set forth in S. 1283; furthermore, w recommend serious consideration be given to e panding the toxicity standards to a degree co parable to those set forth in Article 173, the hazar ous substances provision of the New York Ci Health Code.

The other provision of S. 1283 on which we wi to comment concerns the scope of the bill. O original statement recommended that it include hazardous substances "distributed as packag chemicals for non-manufacturing purposes" rath than those "intended or suitable for househo use." At the hearing, Mr. Nicholas Walker, repr senting the Manufacturing Chemists Associatio implied that it is not feasible to include househol commercial, and industrial chemicals in the sa bill because their labels will vary. However, admitted that the principles used in preparing pr cautionary labelling for these three types of chem cals are the same. The argument against combini labelling for these chemicals in one bill is no mo valid here than it would be if applied to the Fe eral Food, Drug and Cosmetic Act which regulat three different types of chemical containi products.

The phrase, "suitable for household use," to defi the scope of the proposed legislation maintains th same inherent weakness which brought criticism the Federal Caustic Poisons Act. The restricti scope and language of this statute is the basis f the dissatisfaction with Caustic Poison Laws. T continue it under the guise of new and improve legislation is hardly a step forward and certain will not meet the compelling need for better co trol of hazardous substances.

If the American Medical Association can be further assistance to you or your Committee in yo consideration of S. 1283, 86th Congress, please fe free to call on us.

Sincerely yours,
F. J. L. Blasingame, M.D.
Executive Vice-President.

MEDICINE AND THE LAW

QUESTIONS AND ANSWERS ON INCOME TAX

Q. I plan to attend three medical meetings in Europe on May 15, May 28, and June 10. These meetings involve my medical specialty. Since it is more economical for me to remain in Europe during the interim between these meetings than to make separate trips, I will spend the open periods in sightseeing. What expenses may I deduct?

A. If a taxpayer travels to a destination and while at such destination engages in both business and personal activities, traveling expenses are deductible only if the trip is related primarily to the taxpayer's business or the practice of his profession. The Internal Revenue Service has taken the position that whether a trip is related primarily to the taxpayer's business or profession or is primarily personal depends on the facts and circumstances in each case. The amount of time during the period of the trip which is spent on personal activity compared to the amount of time spent on activities directly related to the practice of the traveler's profession is an important factor in determining whether the trip is primarily personal. The staggered dates of the meetings are an important consideration in establishing that your trip is primarily for business and not for personal reasons since most of your time in Europe will not be devoted to attending meetings. However, under no circumstances will you be allowed to deduct your sight-seeing and other personal expenses. Deductible traveling expenses include travel fares, meals, lodging, tips, and such other traveling expenses as are reasonable and necessary in your business travel.

Q. I am a medical specialist and my patients are frequently referred to me by other physicians. For business reasons, I sometimes entertain these physicians. To what extent are my entertainment expenses deductible?

A. A physician may deduct the costs of entertainment, provided he can establish, by appropriate evidence, that such expenses are ordinary and necessary business expenses and clearly related to the production of business income. You must be able to show the business benefit reasonably expected from the expenditure. The general statement that you hope to get referrals as a result of the entertainment is not enough. The following are typical criteria which I. R. S. uses in determining the deductibility of entertainment expenses by a physician: (1) the nature of your practice, (2) the names of the individuals entertained, as shown by your records, and the reason why additional income could reasonably be expected by entertaining these persons, (3) whether or not referrals were actually received from the doctors entertained, (4) the number of times individual doctors were entertained during the year, inasmuch as repeated entertainment indicates, in the opinion of I. R. S. a personal motive, and (5) whether or not other doctors in the same type practice in the locality have entertainment expenses.

Q. I have two automobiles. One automobile I use exclusively in my practice, and the other my wife and I use for personal travel. Is the I. R. S. correct in disputing my claim for 100% of the expense of the automobile which I use in my practice?

A. To the extent that you use your "business" automobile for commuting to and from "work" this constitutes a personal and not a business use. This is the same rule which prohibits your secretary or office nurse from deducting her transportation costs to and from work. If, for example, you drive your business automobile 10,000 miles during the year and 1,000 miles is estimated as attributable to commuting between your home and office, you would be entitled to deduct 90% of the cost of operation as a business expense. Commuting includes the first trip away from home and the last trip home each day.

Q. My health does not permit me to drive an automobile when I make house calls. After school hours, my son works for me as a chauffeur and I pay him for his services. Is his salary deductible?

A. A physician may employ a member of his family as a chauffeur, nurse, etc., in his practice and deduct the compensation paid provided that there is a genuine employer-employee relationship. The deduction should not exceed the amount that would have been paid to a stranger for similar services. A Treasury ruling holds, however, that if the father requires the child to purchase his own clothing or other necessities which the father is obligated to purchase, the deduction of the child's earnings should be disallowed to that extent.

Q. What is the current status of the tax law with regard to postgraduate courses?

A. A practicing physician may deduct his expenses in taking courses in order to maintain the existing kind of practice in which he is engaged, as contrasted with those courses taken for the purpose of beginning specialty practice. Expenses involved in taking the latter courses do not constitute a deductible expense. If your purpose in taking a course is primarily to keep abreast of new developments so as to maintain your existing practice, the expenses incurred are deductible. These expenses include tuition, travel, meals, and lodging while away from home.

Q. Occasionally, I see patients at my home. I have also set aside a room as a study for keeping up-to-date on medical literature. What portion of my household expenses may I deduct?

A. Under these facts it is doubtful whether any portion of your household expenses would constitute a legitimate deduction. If you use part of your residence as your principal office or a bona-fide second office, you are entitled to a business deduction for those expenses, on a pro-rata basis, which are properly attributable to the portion of your residence which is used as an office. For example, if one room in a seven-room rented house is used as your office, you would be entitled to deduct one-seventh of your rent, heat, light, fire insurance, etc. If your household maid also cleans your office, you may estimate the portion of her working time which is devoted to cleaning your office and deduct this portion of her wages. In the event that you own your residence you may similarly take a depreciation deduction on a pro-rata basis. In the event that you are questioned by a government agent as to whether you maintain a bona-fide second office in your residence, you must be prepared to show that you regularly see patients and maintain adequate treatment facilities at your home.

Q. I plan to take my wife with me to the A. M. A. Annual Meeting in Miami this June. May I deduct her expenses?

A. The I. R. S. has held such expenses to be personal and therefore nondeductible.

Q. Am I entitled to deduct my wife's expenses as a member of my medical association's women's auxiliary?

A. In a Tax Court case, a physician was denied a deduction for the expenses incurred by his wife as a member and officer of a medical association's women's auxiliary on the basis that he could not establish a positive economic benefit to his practice as a result of her membership.

Q. I am planning to take a "medical" cruise in the Caribbean which will feature a daily program of discussions and lectures on medical topics. Are my expenses deductible?

A. Treasury agents are prone to scrutinize such deductions carefully. The opportunities for recreation on a cruise of this nature are obvious and it is most difficult to convince an agent under these circumstances that the primary purpose is educational rather than personal. As a practical matter, agents will frequently compromise and permit partial deductions not exceeding 50% of the cost.

Q. In order to take advantage of the long-term rate, I purchased a three-year fire insurance policy covering my office equipment. Is the total premium deductible this year?

A. The I. R. S. has taken the position that the deduction for the premium paid for a long-term policy must be spread proportionately over the term of the policy. Therefore, you may deduct only the earned portion of the premium this year and the remaining premium cost in the years that it is earned by the insurance carrier. However, the premium covering insurance for a term of one year or less may be deducted in the year paid even though the policy may expire the following year.

Q. My professional liability insurance carrier, the British Commercial Insurance Co., is now in liquidation and it appears that I may have to contribute toward the settlement of a claim against me which is now being negotiated. Is this deductible?

A. You are entitled to deduct as a business expense, in the year paid, any payments made for the purpose of settling or paying a professional liability claim or judgment. If any portion of the payment is later recovered by you from the liquidators of the company, this will have to be reported as income.

Q. During the year, I paid a number of fines for parking. These were incurred while I was making house calls. Are they deductible?

A. Traffic fines are not deductible.

Q. Is the cost of an air conditioner or a special mattress deductible as a medical expense?

A. Portable room-type air-conditioning units installed on the advice of a physician for the purpose of alleviating allergies, respiratory, or similar ailments, may be deducted as a medical expense. However, air-conditioning systems which are built into the premises as permanent improvements may not be deducted. The cost of a special mattress, prescribed by a physician and intended to relieve an arthritic or similar condition, is a valid medical deduction.

Q. My wife's illness has made it necessary for me to employ a housekeeper so that she may have the rest necessary for her recovery. Is this a deductible expense?

A. The wages of a housekeeper employed to relieve your wife of household chores is not a deductible item. However, if your housekeeper's duties also include nursing services to your wife, a portion of her wages may be deducted on a reasonable pro-rata basis as a medical expense.

Q. One of my patients is so handicapped that it is necessary for him to commute to and from work in a taxi. Is the fare deductible either as an expense of his employment or as a medical expense?

A. Commuting to and from work is not deductible as a business expense even though the physical handicap of your patient does not permit him to use normal transportation. However, a recent court decision holds that where the employment is solely for therapeutic reasons, the transportation costs may be deducted as a medical expense.

MEDICAL NEWS

COLORADO

Dr. Kempe Studying Smallpox in India.—Dr. C. Henry Kempe, head, department of pediatrics, University of Colorado School of Medicine, Denver, has gone to Madras, India, where he will continue his studies on the prevention of smallpox under the auspices of the World Health Organization for a six-week period beginning March 1. His research will be conducted at the King's Institute, a medical research center near Madras, and will include a continuation of his work with hyperimmune vaccinal gamma globulin. Dr. Kempe, a consultant on smallpox to the World Health Organization, conducted similar studies in India six years ago. He will return to the University of Colorado Medical Center on April 15. Joining Dr. Kempe at Madras for the research program will be Prof. Allan W. Downie, University of Liverpool, Liverpool, England; Miss Cynthia Bowles, recently graduated registered nurse, of Connecticut, daughter of U. S. Representative Chester Bowles, former Ambassador to India; and Mrs. Leone St. Vincent, research associate, University of Colorado School of Medicine, department of pediatrics. When Dr. Kempe leaves Madras early in April he will be replaced by Dr. Gordon Meiklejohn, head of the department of medicine, University of Colorado School of Medicine, and Dr. Trygve Berge of Walter Reed Army Medical Center, Washington, D. C., who will continue the smallpox research program for four weeks.

CONNECTICUT

Establish Department of Science History.—President A. Whitney Griswold of Yale University announced Feb. 19 that a new department of history of science and medicine will be established and will offer both undergraduate and graduate courses beginning next September. Faculty appointments to the new department include Dr. John F. Fulton, Sterling Professor of the History of Medicine, as chairman; Mr. Derek J. deSolla Price, British scientist and historian, to the newly-created professorship of the history of science and also as curator of scientific instruments; and Mr. Leonard G. Wilson, appointed assistant professor of the history of medicine. The new department will be part of both the Yale Graduate School and the School of Medicine, and will replace the present history of medicine department which operates chiefly within the medical school.

FLORIDA

Hospital Seminar in Miami.—The 10th annual postgraduate seminar, conducted by the Mount Sinai Hospital of Greater Miami, will be held May 12-14 at the Hotel Fontainebleau. Guest speakers include Drs. Sol Sherry, St. Louis; Harold L. Israel, Philadelphia; Philip Thorek, Chicago; Edward R. Woodward, Gainesville; Jack E. Berk, Detroit; Edward A. Gall, Cincinnati; Robert B. Greenblatt, Augusta, Ga.; and David E. Zion, Los Angeles.

ILLINOIS

Cancer Congress Held in Springfield.—On March 9-11 the first Illinois Cancer Congress was presented in Springfield by the Illinois Department of Public Health in cooperation with the American Cancer Society, Illinois Division, the Illinois Academy of General Practice, and the Illinois State Medical Society. Speakers at the general sessions included the following: Dr. Warren H. Cole, Chicago; Dr. Leona Baumgartner, New York City; Dr. Donald L. Paulson, Dallas, Texas; Dr. Edward L. Burns, Toledo, Ohio; Dr. Nathan N. Crohn, Chicago; Dr. I. Phillips Frohman, Washington, D. C.; Dr. Emerson Day, New York City; and Dr. Lloyd M. Graves, Memphis, Tenn. Eight clinical conferences were held concerning the early detection of cancer of the skin, mouth, lungs, breast, uterine cervix and corpus, genital and urinary organs, rectum and colon, and thyroid. Information concerning the meeting may be obtained from the Illinois Department of Public Health, Division of Hospitals and Chronic Illness, Room 518, State Office Building, 400 S. Spring St., Springfield, Ill.

Chicago

Dr. Pinkus to Give Pusey Lecture.—Dr. Herman K. B. Pinkus, Monroe, Mich., will give the annual William Allen Pusey Lecture of the Chicago Dermatological Society on Wednesday, March 16, at the Illini Union, 715 S. Wood St., at 7 p. m. Preceding the lecture, dinner will be served at 6 p. m. at the Illini Union. The title of the lecture will be "Four-Dimensional Histopathology."

Personal.—Dr. Edward J. Beattie Jr., chairman, department of surgery, Presbyterian-St. Luke's Hospital, was named vice-chairman of the medical and nursing services of the Chicago Chapter of the American Red Cross. Dr. Beattie will be in charge of recruiting doctor-nurse teams for disaster operations in the area.——Dr. Charles B. Huggins, director of the Ben May Laboratory for Cancer Re-

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

search, University of Chicago, was elected honorary fellow of the Royal College of Surgeons, England, on Dec. 10.

MARYLAND

Dr. Romansky to Lecture.—The Phi Delta Epsilon Graduate Medical Fraternity will hold its annual Aaron Brown Lectureship at the Gordon Wilson Hall in University Hospital, Baltimore, Monday, April 4, 8:30 p. m. Dr. Monroe J. Romansky will deliver a lecture, "Basic Principles in the Use of Chemo-Therapeutic Agencies." Dr. Romansky is professor of medicine, George Washington University School of Medicine, Washington, D. C. He is a diplomate of the American Board of Internal Medicine.

Program for Research in Mental Retardation.—A grant of $1,261,448 to the Johns Hopkins Medical Institutions to establish a research program into the causes of mental retardation and to aid in the construction of the Children's Medical Center was announced Feb. 20 by the president of the Joseph P. Kennedy Jr. Foundation. The grant provides one million dollars for a period of 10 years for research into the etiology of mental retardation, including financial support of up to $15,000 annually for each of five senior research scholars; $150,000 toward the construction of 10 beds and their related hospital facilities in the Children's Medical Center; and $111,448 toward construction of a laboratory floor in the Children's Medical Center to be known as the Lt. Joseph P. Kennedy Jr. Laboratories for Research in Mental Retardation. Dr. Robert E. Cooke, professor of pediatrics and pediatrician-in-chief at the Johns Hopkins Hospital, will head the Kennedy research program. The Kennedy Foundation was established about 15 years ago by Joseph P. Kennedy, former ambassador to Great Britain, in memory of his son, Lt. Joseph P. Kennedy Jr., who was killed in action in World War II.

MASSACHUSETTS

Break Ground for Health Center.—Informal groundbreaking ceremonies for the 10-story University Health Center and office building for Harvard took place Feb. 17 in the parking lot on the corner of Holyoke and Mount Auburn Streets, Cambridge. The Building is scheduled for occupancy in the fall of 1961. Dr. Arlie V. Bock, who directed student health service from 1935 to 1954, broke ground for the new structure. He is Henry K. Oliver, Professor of Hygiene, Emeritus. The structure is the first phase of a planned rebuilding of the block near Harvard Square.

MISSOURI

Hospital Alumni Meeting.—The St. Louis City Hospital Alumni Association will hold its 72nd annual meeting on Wednesday, March 16, at the Le Chateau Restaurant, 10405 Clayton Road, St. Louis County. The Missouri State Medical Association will be meeting in St. Louis at the same time, so alumni of the hospital will be able to attend this annual dinner party. For information, write Dr. Shale M. Rifkin, Suite 830, 3720 Washington Blvd., St. Louis 8.

Annual State Meeting in St. Louis.—The 102nd annual meeting of the Missouri State Medical Association will be held at the Sheraton-Jefferson Hotel, St. Louis, March 13-16. The program includes refresher courses, March 14, and a clinical pathological conference, March 15. Papers to be presented by out-of-state speakers include the following:

Newer Concepts in Therapy of Diabetes, Dr. Franklin B. Peck, Indianapolis.
Surgery of the Common Bile Duct, Dr. George A. Hallenbeck, Rochester, Minn.
Estimation and Measurement of Blood Loss at Delivery Dr. Michael Newton, Jackson, Miss.
Pulmonary Emphysema, Dr. Hurley L. Motley, Los Angeles.
Indications for Open Heart Surgery in Adults, Dr. Ormand C. Julian, Chicago.

Two panel discussions are planned: "Medical Insurance, To Whom Does the Fee Belong?" and "Peripheral Vascular Disease." On March 16 a seminar "Accidents in Children," and a symposium, "Modern Concepts of Treatment of Arteriosclerotic Heart Disease," will be held concurrently. At the annual banquet 7:30 p.m., March 15, Congressman Bruce Alger, of Texas, will be the speaker.

NEBRASKA

Regional Meeting of Physicians.—The 14th annual regional meeting of the American College of Physicians for Nebraska will be held March 19 at the Cornhusker Hotel, Lincoln. Dr. Howard P. Lewis, Portland, Ore., president of the college, will present "The Role of the College in the Progress of Medicine" at the banquet, 6:30 p.m., and will speak on "Some Interesting Features of the Differences in Human Constitution" during the afternoon. The program includes the following papers:

Sodium Chloride and Potassium Losing Syndrome in Surgically Induced Diabetes Insipidus, Dr. William J. Dickerson, Omaha.
Experience with Phenformin, Dr. Maurice L. Pepper, Omaha.
Drug Induced Hemolytic Anemia, Dr. James A. Mailliard, Omaha.
Chromogen Infection of Lung, Dr. Orest J. Parillo and Dr. Morris Meiberger, Omaha.
A Comparison Between Peritoneal *Dialysis* and Hemo-Dialysis (Artificial Kidney), Dr. Charles F. Gutch, London.

Governor of the college for Nebraska is Dr. Edmond D. Walsh. For information, write the American College of Physicians, 4200 Pine St., Philadelphia 4.

NEW YORK

Program for Hospital Administrators.—A four-week Hospital Administrators Development Program will be offered at Cornell University, Ithaca, from July 11 to Aug. 5. The program will "offer hospital administrators an opportunity to add to their professional knowledge, explore new developments in hospital administration, and broaden their points of view." About 25 hospital administrators will be selected on the basis of applications received. The brochure and application blank may be obtained by writing to the Sloan Institute of Hospital Administration, Graduate School of Business and Public Administration, Rand Hall, Cornell University, Ithaca, N. Y.

New York City

Symposium on Fibrinolysis.—A symposium on fibrinolysis sponsored by Sloan-Kettering Institute will be held on March 25-26 at the Waldorf-Astoria Hotel. The program will cover the basic work on plasminogen, the activators and inhibitors of the fibrinolytic system, animal and physiological studies, and clinical experience with these materials. For information, write Dr. Eugene E. Cliffton, Sloan-Kettering Institute for Cancer Research, 410 E. 68th St., New York 21.

Clinic for Hearing and Speech.—A hearing and speech clinic was formally opened at the Kings County Hospital Center, Brooklyn, Feb. 24 by the department of hospitals of the City of New York. The clinic, under the supervision of Dr. Ira A. Polisar, director of otorhinolaryngology at the hospital and head, division of otorhinolaryngology, State University of New York Downstate Medical Center, will be open five days a week for the diagnosis and treatment of hearing and speech problems in patients of all ages. Services will include the diagnosis of hearing disorders, the prescription and evaluation of hearing aids, surgical correction of hearing loss if indicated, evaluation of disorders of speech, audiometric training, and speech therapy. A research program is also anticipated.

NORTH CAROLINA

Establish Neurology Department at Bowman Gray.—A new department of neurology for the Bowman Gray School of Medicine of Wake Forest College has been established. Dr. Martin G. Netsky, professor of neurology and neuropathology and associate in physiology and pharmacology, was named director of the department. Prior to becoming a separate department, neurology was a division of the combined department of psychiatry and neurology. In announcing future plans for the new department, Dr. Netsky lists its primary objectives as follows: (1) to train neurologists for further academic work; (2) to create a base for research in neurology; and (3) to develop a broad program of neurological sciences in all of the phases of medical instruction throughout the medical school. This will include neurology, neuropathology, neuropharmacology, and other areas.

OHIO

Law-Medicine Institute in Cleveland.—The Western Reserve University Law-Medicine Center in Cleveland will hold a two-day institute, "Alcohol Intoxication and Influence," May 12 and 13. The institute will emphasize the civil and criminal aspects of the topic and will consider such areas as the physiological effects of alcohol on the human body, the history and theory of chemical tests, and the scientific equipment available to perform chemical tests. Also under discussion will be the preparation of civil and criminal cases involving the issues of intoxication and influence. A segment of a criminal trial involving the intoxication issue in a traffic manslaughter charge is planned. The lectures and demonstrations will be provided by members of the Western Reserve University faculty and the professional staff of the Cuyahoga County Coroner's Office along with public officials. The enrollment fee is $25. For registration or information, contact Oliver Schroeder Jr., Director, the Law-Medicine Center, 2145 Adelbert Road, Cleveland 6.

WYOMING

Report on Births.—The Wyoming Department of Public Health in its monthly *Good Health for Wyoming* announced that 8,019 new births were reported in the state in 1959, an increase over the 7,950 births registered in 1958. This reverses a trend of decreasing births which started in 1955. The 2,644 deaths reported in 1959 also exceeded the 2,572 registered in 1958. Only in 1957 has this number been exceeded in Wyoming, the number being 2,666.

GENERAL

Conference on Vascular Disease of the Brain.—On Saturday afternoon, April 30, and Sunday morning and afternoon, May 1, the American Academy of Neurology is sponsoring an International Conference on Vascular Disease of the Brain. The conference will be held immediately following the close of the regular scientific sessions of the academy and will be open to the medical profession. This conference is being supported by the National Institute of Neurological Disease and Blindness and will be divided into three sections dealing with experimental studies, diagnostic procedures, and therapy. The conference will be held at the Eden Roc Hotel, Miami, Fla., headquarters for the academy meetings.

Meeting of Neuropsychiatric Hospital Association.—The 1960 annual meeting of the Central Neuropsychiatric Hospital Association will be held Thursday and Friday, March 17-18, at the Bismarck Hotel, Chicago. There will be medical, business, and social-work sections. The guest speaker for the main luncheon will be Dr. Lewis L. Robbins, medical director, Hillside Hospital, Glen Oaks, N. Y., whose topic will be "The Acting-Out Patient in the Private Psychiatric Hospital." For information, write Dr. Ralph S. Green, The Haven Sanitarium, Inc., Rochester, Mich., Secretary-Treasurer.

Meeting of Northwest Psychiatrists.—The North Pacific Society of Neurology and Psychiatry, in conjunction with the Northwest District Branch of the American Psychiatric Association, will hold its annual scientific meeting at the Benjamin Franklin Hotel, Seattle, April 8 and 9. Guest speakers will be Dr. Douglas D. Bond, chairman, department of psychiatry, Western Reserve School of Medicine, Cleveland, and Horace Magoun, Ph.D., head, department of anatomy, University of California, Los Angeles. For information, write Dr. Thomas H. Holmes III, Department of Psychiatry, University of Washington, Seattle 5, Secretary-Treasurer.

Aerospace Meeting in Miami Beach.—Dr. Ludwig G. Lederer, Washington, D. C., president, Aerospace Medical Association, announced that Detlev W. Bronk, Ph.D., president of the Rockefeller Institute and of the National Academy of Sciences, will present the sixth Louis H. Bauer Lecture at the association's 31st annual meeting at the Americana Hotel, Miami Beach, Fla., May 9-11. More than 100 papers, "covering all aspects of aerospace medicine and research," comprise the scientific program of the meeting. Dr. Lederer is medical director of Capital Airlines and physician-in-chief of the Washington National Airport. At the close of the 1960 meeting the association will install as its new president Dr. George J. Kidera, of Chicago, medical director of United Air Lines. For information, write Dr. Robert J. Benford, 4200 Cathedral Ave., N. W., Washington 16, D. C.

Increase in Contributions to Education Foundation.—The conclusion of the 1959 year found "a marked increase" in funds contributed by physicians to medical education through the American Medical Education Foundation. The foundation closed the 1959 books on Jan. 31, 1960, with a total of $1,195,824.79, an increase of $75,780.10 over the 1958 total which included a gift from the American Medical Association of $100,000. The total increase in contributed money is $175,780.10, or a 17.2% increase over the contributed amount of the preceding year, not including the A. M. A. grant. The two-year increase in the actual amount of contributions, discounting A. M. A. grants, is 36.7%. Forty-one state and Puerto Rico increased their total contribution during 1959 over that of 1958. The total number o contributors increased from 49,729 in 1958 t 55,399 in 1959.

Intermountain Pediatric Meeting.—The annual clinical convention of the Intermountain Pediatric Society will be held at the Stardust Hotel, Las Vega Nev., March 28-29. Dr. Lloyd G. Veasy, Salt Lak City, president of the society, will open the progra with an address. Each of the following three gues speakers will present two papers: Dr. Robert Cooke, professor of pediatrics, Johns Hopkins Un versity School of Medicine, Baltimore; Dr. Lou K. Diamond, associate professor of pediatrics, Ha vard Medical School, Boston; and Dr. Frederic Silverman, associate professor of radiology an pediatrics, University of Cincinnati College Medicine. Round-table discussions will be co ducted at the luncheon sessions both days. Regi tration fee is $25, and the meeting is open to a interested physicians. A ladies' luncheon is planne for March 29. For information, write the Inte mountain Pediatric Society, 2000 S. 9th East Stree Salt Lake City, Utah.

Public Relations Institute for Health Personnel. A first-time Public Relations Institute for healt and welfare agency personnel will be held in Ne York City June 2 and 3 by the National Publici Council for Health and Welfare Services. Geared agency administrators as well as to public relatio and education staffs and volunteers on the loca state, and national levels, the institute will de with the public relations problems of administrato and others having major public relations respons bility and with the "latest thought and practice" i public relations planning and evaluation. Progra speakers will be drawn from both the nonprofit an commercial public relations fields. Registration fe for the two-day institute, which will be held at th Hotel Belmont Plaza, is $10 for persons in membe agencies of the National Publicity Council, and $1 for others. Advance registration is required. Alon with the National Publicity Council, the institute i being sponsored by two-score national and loca health and welfare agencies, all sustaining membe of the council. For information or advance registration, write the council at 257 Fourth Ave., Ne York 10.

Plural Births.—Statisticians of the Metropolitan Lif Insurance Company report that plural births are relatively uncommon occurrence. Of the abou 27,700,000 confinements in the United States durin the seven-year period 1951-1957, less than 300,00 resulted in a plural birth in which at least one infant was born alive, a frequency of a little more than 10 per 1,000 confinements. For every million confinements in the period under review, there were 10,539 pairs of twins, 93 sets of triplets, and only about 1 set of quadruplets. The likelihood that a confinement will result in a plural birth varies with the age of the mother. The chances are smallest for teen-age mothers—6 per 1,000—and increase with advance in age to a maximum of about 16 per 1,000 at ages 35-39. Women in this age group accounted for little more than 8% of all confinements, but for 13% of the twins and 17% of the triplets born during 1951-1957. The chances that the confinement of a woman aged 40-44 will result in a plural birth are nearly 13 per 1,000 and for those at the end of the reproductive period the chances are about 8 per 1,000. The relative frequency of plural births are 14 per 1,000 for nonwhite and 10 per 1,000 for white women.

Report on Venereal Disease.—The Annual Joint Statement on Today's Venereal Disease Control Problem, sponsored by the American Social Health Association, the Association of State and Territorial Health Officers, and the American Venereal Disease Association, and developed from information provided by the health departments of all 50 states, 3 counties, 91 cities with population over 100,000, and the District of Columbia, was released Feb. 23. The number of early infectious syphilis cases reported increased from 6,661 in 1958 to 8,178 in 1959, or 22.8%. Gonorrhea cases rose from 220,191 in 1958 to 237,318 in 1959, or 7.8%. First quarter reports for fiscal 1960 show 42% more cases of early infectious syphilis than for the same period last year. Data received from the British Isles also indicated a "significant rise" in venereal disease. The British Cooperative Clinical Group reports increases in all ages for males through 59, and in all ages except 35-49 for females.

Venereal disease is up 14.3% in the 10-14 age group over 1958 and 11.4% in the 15-19 group. The statement points out the greatest concentration of reported venereal disease in all age groups is in cities having populations over 100,000. In New York City, early infectious syphilis is up 59.6% in the 10-14 age group and 78.3% in the 15-19 group. The statement indicated that syphilis kills a minimum of 4,000 persons a year, and costs $12,000,000 a year to maintain the syphilitic blind and $46,000,000 for hospitalization of syphilitic psychotics. Of untreated syphilitics, 1 in 200 will become blind; 1 in 50 will become insane; 1 in 25 will become crippled or incapacitated to some extent; and 1 in 15 will become a syphilitic heart victim.

General Practice Meeting in Philadelphia.—The American Academy of General Practice annual scientific assembly will be held March 21-24 in Philadelphia. The four-day scientific program, in Convention Hall, will feature 35 prominent speakers, 127 scientific and 219 technical exhibits. A complete modern office building will be erected inside Convention Hall and will contain complete examination and diagnostic facilities, laboratory equipment, two offices, and a waiting room. The building will be erected by the Sears Roebuck Foundation as part of its program to help find doctors for small rural communities, A mid-19th Century doctor's office, will be located adjacent to the Sears Foundation building. The academy's policy-making Congress of Delegates will meet at 2 p. m., March 19, in the Bellevue-Stratford Hotel. The scientific program will open at 1:30 p. m., March 21, with a panel discussion of the doctor-patient relationship and the related role of the doctor's wife. Two geriatric sessions will follow. Sessions will include the following topics; antibiotic therapy, preventive pediatrics, old and new concepts of the origin of disease, gynecologic surgery, occupational health, cardiac emergencies, traumatic cerebral emergencies, hematology, and mental health. Social activities include the president's reception and dance and a ladies' program. Twenty $1,000 general practice residency training awards will go to interns or young physicians who have completed their military training. The assembly is combined with the Philadelphia Postgraduate Institute. For information, write the American Academy of General Practice, Volker Boulevard at Brookside, Kansas City 12, Mo.

FOREIGN

Meeting of German Otorhinolaryngologists.—Prof. Meyer zum Gottesberge, Secretary, Deutsche Gesellschaft der Hals-Nasen-Ohrenärzte, Düsseldorf Moorenstr, 5, Germany, announced that the German Society of Otorhinolaryngologists will hold their annual meeting May 25. The chief subjects are allergy from the viewpoint of the otolaryngologist, the malignant tumors of the mesopharynx, and the irradiation of malignant tumors of the mesopharynx.

Neuropathology Congress in Munich.—The fourth International Congress of Neuropathology will be held in Munich, Germany, Sept. 3-8, 1961. The main themes are histochemistry and related biochemistry of diseases of the central and peripheral nervous systems (Sept. 4); electron microscopy of the central and peripheral nervous systems and of the myoneural junction (Sept. 5); cell biology and cell culture of nervous tissue (Sept. 6). Deadlines for abstracts for these themes is June 1, 1960. There will also be groups of papers on perinatal neuropathology and free papers. Those wishing to attend should notify the chairman of the American committee, Dr. Orville T. Bailey, Neuropsychiatric Institute, 912 S. Wood St., Chicago 12.

CORRECTIONS

Diagnostic Approach to the Infant with an Enlarging Head.—In the article entitled "Diagnostic Approach to the Infant with an Enlarging Head" in The Journal, Feb. 6, page 538, an error appeared. The illustration on page 540 was printed upside down. The legend, to be meaningful, must be placed on the opposite side of the illustration.

Hypothermic Coma.—In the letter from the United Kingdom, "Hypothermic Coma from Chlorpromazine," in The Journal, Jan. 23, page 367, it was stated that a patient was immersed in a water bath at 98 C. This should have read 98 F. The reference cited should have been the *British Medical Journal* and not *Lancet*.

Annual Lecture in Chicago March 30.—Dr. Joseph H. Kiefer, chairman of the Committee on the Annual D. J. Davis Memorial Lecture on Medical History has reported that the news item published in The Journal for Feb. 13 under Chicago announcing the Davis Lecture should have read March 30 as the date of the lecture. Also the room number should have been 106 of the Dental-Medical-Pharmacy Building of the University of Illinois, 1853 W. Polk St., Chicago.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

American Board of Anesthesiology: *Written.* Various locations, June 24. Final date for filing application was January 10. *Oral.* Miami Beach, April 25-30. Applications already on file. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

American Board of Dermatology: *Written.* Various locations, June 5, 1961. Final date for filing application is March 1, 1961. *Oral.* Philadelphia, Oct. 13-16. Sec., Dr. Beatrice M. Kesten, One Haven Ave., New York 32, New York.

American Board of Internal Medicine: *Oral.* San Francisco, March 30-April 1; New York City, Nov. 14-17. Closing date for filing application: Jan. 2 and July 1. *Written.* Oct. 17. Closing date for filing application is May 1. *Oral. Gastroenterology.* Philadelphia, March 11-12. Final date for filing application was January 15. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

American Board of Neurological Surgery: Examination given twice annually, in the spring and fall. St. Louis, April 10-12. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

American Board of Obstetrics and Gynecology: *Part II Oral and Clinical.* Chicago, April 11-16. Final date fo filing application was August 1. Applications for certification in Part I, new and reopened, and requests for reexamination in Part II are now being accepted. Deadlin for receipt of applications is August 1, 1960. After July 1 1962 a minimum of three years of approved progressiv residency training will be required. Training by preceptorship will no longer be acceptable. The initiation o preceptorships will not be approved after July 1, 196 Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

American Board of Ophthalmology: *Written.* Jan. 2 1961. Deadline for filing applications is July 1. *Oral.* Sa Francisco, May 9-13; Chicago, Oct. 3-7. Sec., Dr. Merri J. King, Box 236 Cape Cottage Branch, Portland, Main

American Board of Orthopaedic Surgery: *Part I,* Nashville, Denver and Philadelphia, Apr. 13-14. Deadline f receipt of applications was Nov. 30. *Oral and Writte Part II.* Miami Beach, Jan. 3-5, 1961. Final date for filin application is July 1. Sec., Dr. Sam W. Banks, 116 Sout Michigan Ave., Chicago 3.

American Board of Otolaryngology: *Oral,* Chicago, Oc 3-6. Final date for filing application is April 1. Sec., D Dean M. Lierle, University Hospitals, Iowa City.

American Board of Pathology: Memphis, April 21-2 Final date for filing application was March 7. *Examination in Forensic Pathology.* Memphis, April 22. Final da for filing application was March 7. Sec., Dr. Edward Smith, Indiana University Medical Center, 1100 W Michigan St., Indianapolis 7.

American Board of Pediatrics: *Written.* New York Cit January 1961. Final date for filing application is Dec. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemon Pa.

American Board of Physical Medicine and Rehabilitation: *Oral and Written.* New York, June 17-18. Sec., D Earl C. Elkins, Mayo Clinic, Rochester, Minn.

American Board of Plastic Surgery: *Oral and Writte* Milwaukee, May 1960. Final date for filing applicatio was January 1. Corresponding Secretary, Mrs. Estelle Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

American Board of Proctology: *Oral and Written, Par I and III,* Philadelphia, Sept. 24. Final date for filin application is June 30. Sec., Dr. Stuart T. Ross, 52 Franklin Ave., Garden City, N. Y.

American Board of Psychiatry and Neurology: Ne York, New York, Dec. 12-13. *Child Psychiatry.* Chicag April 25-26. Sec., Dr. David A. Boyd, Jr., 102-110 Secon Ave., S.W., Rochester, Minn.

American Board of Radiology: *Examination.* Cincinnat June 6-10; Dec. 5-9. Deadline for filing applications f the June examination was Jan. 1. Filing deadline for th December examination is July 1. A special examinatio in *Nuclear Medicine (for those diplomates in Radiolog* or Therapeutic Radiology) will be offered provided ther are sufficient applications. Sec., Dr. H. Dabney Ker Kahler Hotel Bldg., Rochester, Minn.

American Board of Surgery: *Oral Examinations (Part II)* Kansas City, Kans., May 16-17, and Los Angeles, Ma *19-20. Sec., Dr. John B. Flick,* 1617 Pennsylvania Blvd Philadelphia 3.

Board of Thoracic Surgery: *Oral.* May 1960. Final dat for filing application was Dec. 1. Sec., Dr. Wm. M. Tuttle 1151 Taylor Ave., Detroit 2.

American Board of Urology: *Written.* December. *Oral Clinical.* Chicago, February 1961. Exec. Sec., Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 26.

GOVERNMENT SERVICES

AIR FORCE

General Powell Awarded Legion of Merit.—Major Gen. William H. Powell Jr., assistant to the surgeon general, U. S. A. F., was awarded the Legion of Merit recently in ceremonies held in Washington, D. C., prior to his retirement on Jan. 31. The award was presented for his outstanding service to the United States while serving as chief medical officer, upreme Headquarters Allied Powers Europe, from uly 3, 1957, to Sept. 3, 1959. He was cited for his utstanding leadership, exemplary foresight, and ceptional judgment in resolving medical and gistic support problems of the various national rces within Allied Command Europe.

ir Force Clinical Surgeons Meet.—The annual eeting of the Society of Air Force Clinical Sur- ons will be held at the U. S. A. F. Hospital, avis Air Force Base, Calif., April 13-15, 1960. is meeting will include original papers in various rgical specialties. Moderators and other speakers ve been chosen from among senior Air Force rgeons, national consultants to the surgeon gen- al, and specially invited medical authorities in the n Francisco bay area.

OOD AND DRUG ADMINISTRATION

urt Actions.—In December 42 tons of nuts for e Christmas trade were found insect-infested, oldy, spoiled, shriveled, and with empty shells. cause of rodent contamination 150 tons of bulk eat was seized. Rotten eggs were found in 20 ns of frozen whole eggs intended for commercial od processing, and spoiled chicken was found in tons of cut-up chicken in consumer packages. nong foods taken off the market as hazards to alth were candy suckers with pointed wooden cks that could injure children, wheat in which rcury-treated seed wheat was mixed, and fresh d processed cranberries containing aminotriazole. alth violations were also charged against 148,000 blets of low-strength vitamin products. Seized as onomic cheats were 5 tons of canned freestone aches not labeled to show they were below stand- l in quality.

Of the 11 drugs and devices seized in December, were alleged to be misbranded by false and mis- ding claims. Canned "natural" celery juice was ered as part of a vegetable "juice therapy" pro- am for diseases including arthritis, rheumatism, uritis, chronic appendicitis, high blood pressure, oplexy, and arteriosclerosis. Two makes of so-called air purifiers—portable cabinets into which room air was drawn and caused to flow through an electrostatic field or exposed to ultraviolet light—were seized because of claims that they were effective in treating or preventing hay fever, asthma, sinus trouble, and allergies to airborne substances. Alleged to be adulterated as well as misbranded were 300,000 digitalis tablets that were substantially lower in strength than the 100 mg. claimed on the label.

"Reducing-Aid" Cigarettes.—A federal court decision affirmed the government's view that Trim Reducing Aid cigarettes are not effective for weight reducing and are a "new drug" for which safety has not been established. The tobacco in "Trim" cigarettes contains added amounts of tartaric acid, allegedly an appetite suppressant, and flavoring oils. The product was offered as a new scientific weight-reducing discovery approved by physicians and other scientists after years of clinical testing. According to other promotional claims in the literature of the manufacturer, Cornell Drug Corporation, New York, you could "puff your pounds away" or "watch your weight go up in smoke" by smoking three Trims daily. No attention to the diet was necessary, the promoter said.

Drug Firm Prosecuted for Poor Controls.—Inadequate drug manufacturing controls led to the prosecution of an Iowa firm for shipping a dangerous drug prescribed for reducing weight at two-and-a-half times the strength declared on the label, the Food and Drug Administration reports. Desoxyephedrine hydrochloride, with a strength of 10 mg., was shipped in a drum labeled 4 mg., and the label failed to bear the statement, "Caution: Federal law prohibits dispensing without prescription." On Nov. 2, 1959, Sentral Laboratories, Des Moines, Iowa, and James H. Roberts, president, pleaded guilty to the charges and a fine was imposed.

Physician Convicted and Loses License.—A physician already convicted of selling amphetamine drugs without a proper physician-patient relationship violated the terms of his probation and was sent to prison. On Oct. 29, 1959, Dr. Harry G. Williams pleaded guilty to five counts of dispensing the "pep pills" or "bennies" without prescription and in unlabeled vials. The court fined him $1,000, suspended a one-year jail term, and placed him on probation for three years. Within a month he was charged with violating his probation by selling 1,284 tablets of the same drugs to a drug addict. The physician pleaded guilty and was sentenced to serve the previously suspended jail sentence. The state of Nebraska revoked his license to practice medicine.

DEATHS

Ady, Albert Emmett Ⓜ West Liberty, Iowa; State University of Iowa College of Medicine, Iowa City, 1923; veteran of World Wars I and II; associated with the Mercy Hospital in Iowa City, where he died Dec. 19, aged 63.

Anderson, Lewis Ridley Ⓜ Gainesboro, Tenn.; (licensed by years of practice); past-president of the Jackson County Medical Society; served on the school board of Jackson County; past-president of the Gainesboro Rotary Club; died in the Jackson County Hospital Dec. 14, aged 68.

Bailey, Willard Chapin, San Jose, Calif.; Cooper Medical College, San Francisco, 1899; served as city health officer; for many years member of the board of directors of the San Jose Hospital; twice president of the Chamber of Commerce; died Dec. 18, aged 84.

Barham, Oscar T., Lewisville, Ark.; College of Physicians and Surgeons, Little Rock, 1911; died in Dallas Dec. 19, aged 85.

Barney, J. Dellinger Ⓜ Lenox, Mass.; Harvard Medical School, Boston, 1904; chairman, Section on Urology, American Medical Association, 1931-1932; specialist certified by the American Board of Urology; member of the American Association of Genito-Urinary Surgeons, of which he was past-president, and the American Urological Association; fellow of the American College of Surgeons; member of the honorary staff of the Massachusetts General Hospital in Boston; died in Milton Dec. 15, aged 81.

Bear, Lowery Hartford Ⓜ Vevay, Ind.; Medical College of Indiana, Indianapolis, 1892; served as secretary of the Switzerland County Medical Society; for many years county health officer; died Nov. 26, aged 91.

Billings, Ralph Everett Ⓜ Franklin, Minn.; University of Minnesota Medical School, Minneapolis, 1929; member of the American Academy of General Practice; past-president of the Renville-Redwood Counties Medical Association; past-president of the school board; served as village health officer; died in the Veterans Administration Hospital Dec. 19, aged 69.

Bonar, Elwood D., Columbus, Ohio; Ohio State University College of Medicine, Columbus, 1926; died in the White Cross Hospital Dec. 16, aged 71.

Boyd, Frank Harrison, Opelika, Ala.; Emory University School of Medicine, Atlanta, Ga., 1930; died Dec. 19, aged 54.

Braunlin, William Henry Ⓜ Marion, Ind.; Miami Medical College, Cincinnati, 1904; member of the American Academy of Ophthalmology and Otolaryngology; died in the Marion General Hospital Dec. 22, aged 77.

Brust, Paul Raymond Ⓜ San Diego, Calif.; Stanford University School of Medicine, San Francisco, 1926; served as police department surgeon; formerly on the staffs of the Mercy and Children's Hospitals; died Dec. 26, aged 65.

Buckner, Frank Wooldridge Ⓜ Martinsville, Va.; Duke University School of Medicine, Durham, N. C., 1936; interned at the Duke Hospital in Durham, N. C., and the New Haven Hospital in New Haven, Conn., where he served a residency; served a residency at the Memorial Hospital for the Treatment of Cancer and Allied Diseases in New York City; veteran of World War II; certified by the National Board of Medical Examiners; died Dec. 21, aged 52.

Buckner, Kathryn Ⓜ Philadelphia; Baylor University College of Medicine, Dallas, Texas, 1928; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; served on the faculty of Temple University School of Medicine; associated with St. Christopher's Hospital for Children; died Dec. 28, aged 57.

Burns, Joseph Albert, Little Rock, Ark.; University of Arkansas School of Medicine, Little Rock, 1927; served as a member of the staff of the State Hospital; died Dec. 17, aged 56.

Cady, Laurence Hammond Ⓜ Minneapolis; University of Minnesota Medical School, Minneapolis, 1923; member of the American Academy of General Practice; on the staff of St. Andrew's Hospital; died Dec. 18, aged 68.

Campbell, Eleanor Milbank Anderson, New York City; Boston University School of Medicine, 1916; co-founder and served as director of the Judson Health Center; died Dec. 29, aged 81.

Chaney, Thomas Morris Ⓜ Colonel, U. S. Army, retired, Dunkirk, Md.; University of Maryland School of Medicine, Baltimore, 1906; at one time city health officer of Winston-Salem, N. C.; veteran of World Wars I and II; entered the regular Army

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Ⓜ Indicates Member of the American Medical Association.

in 1921 and retired March 31, 1947; died in the Walter Reed Army Hospital, Washington, D. C., Dec. 29, aged 76.

Clayton, Bonnar Marcus, Birmingham, Ala.; Chattanooga (Tenn.) Medical College, 1908; for many years associated with the Woodmen of the World Hospital in San Antonio, Texas; died Dec. 14, aged 80.

Colman, John Kennedy Ⓜ Butte, Mont.; born in Dunkirk, N. Y., Dec. 31, 1905; University of Michigan Medical School, Ann Arbor, 1931; interned at the University Hospital in Ann Arbor, where he served a residency; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; orthopedic surgeon, crippled children's division, state board of health; chairman of the department of physical medicine and rehabilitation at Butte Community Hospital; associated with the Shodair Crippled Children's Hospital in Helena and St. James Hospital; consultant, Veterans Administration Hospital in Fort Harrison; died Dec. 19, aged 53.

Como, Nicholas Frank Ⓜ Brooklyn; Yale University School of Medicine, New Haven, Conn., 1954; ertified by the National Board of Medical Exminers; served in the U. S. Naval Reserve; on the taffs of the Victory Memorial and Holy Family ospitals; died Dec. 25, aged 29.

Conti, James G. Ⓜ Pittsburgh; Maryland Medical College, Baltimore, 1911; died in the Presbyterian Hospital Dec. 5, aged 72.

Cross, Roland Robert Ⓜ Springfield, Ill.; American Medical College, St. Louis, 1912; past-president f the Jefferson-Hamilton Counties Medical Soiety; spent six years in Indian work; veteran of World War I; formerly superintendent of the health istrict in Southern Illinois; for many years direcor of the Illinois Department of Public Health; ied Nov. 28, aged 71.

Dalton, David, Glenolden, Pa.; Medico-Chirurgical College of Philadelphia, 1908; also a pharmacist; or many years president of the Sharon Hill (Pa.) chool Board and at one time postmaster; served n the staff of the Taylor Hospital in Ridley Park nd the Thomas M. Fitzgerald Mercy Hospital, Darby; died Dec. 28, aged 90.

Davidson, Andrew Blaine Ⓜ San Diego, Calif.; Jeferson Medical College of Philadelphia, 1909; rered from the U. S. Navy Jan. 1, 1943; died in the U. S. Naval Hospital Nov. 20, aged 75.

Denney, Elliott Stevenson Ⓜ Mooseheart, Ill.; Harard Medical School, Boston, 1920; fellow of the American College of Surgeons; medical director at he Philadelphia Memorial Hospital; associated with St. Joseph Mercy Hospital and the Copley Memorial Hospital in Aurora, where he died Dec. 23, aged 67.

Donovan, Paul Royal Ⓜ Medford, Mass.; Tufts College Medical School, Boston, 1925; veteran of World War I; on the staff of the Whidden Memorial Hospital in Everett, New England Sanitarium and Hospital in Stoneham, Mount Auburn Hospital in Cambridge, Winchester (Mass.) Hospital, and the Winthrop (Mass.) Community Hospital; chairman of the medical board of the Lawrence Memorial Hospital, where he died Dec. 22, aged 63.

Drennan, Clyde Leo Ⓜ Polo, Ill.; Northwestern University Medical School, Chicago, 1937; interned at the Evanston (Ill.) Hospital; member of the American Fracture Association; veteran of World War II; member of the Polo Community High School Board of Education; on the staff of the Dixon (Ill.) Public Hospital; died Dec. 18, aged 51.

Du Bois, Paul Walter Ⓜ Detroit; University of Michigan Medical School, Ann Arbor, 1925; fellow of the American College of Surgeons; associated with the Harper Hospital; died Dec. 27, aged 62.

Duffy, Edgar Albert Ⓜ Trenton, Mo.; Marion-Sims College of Medicine, St. Louis, 1899; also a pharmacist; secretary-treasurer of the Grand River Medical Society; member of the American Association of Railway Surgeons; division surgeon for the Rock Island Railroad; president of the staff of the Wright Memorial Hospital, where he died Nov. 28, aged 81.

Dunavant, Andrew Poindexter, Pontotoc, Miss.; Memphis (Tenn.) Medical College, 1910; died in Memphis, Tenn., Dec. 22, aged 70.

Edie, Elliott Bard Ⓜ Uniontown, Pa.; Jefferson Medical College of Philadelphia, 1904; served during World War I and received the Distinguished Service Cross; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; on the staff of the Uniontown Hospital; died in St. John's Hospital, Springfield, Mo., Nov. 26, aged 80.

Farr, Walter John Ⓜ Teaneck, N. J.; Cornell University Medical College, New York City, 1925; veteran of World War II; associated with the Holy Name Hospital in Teaneck, Valley Hospital, Ridgewood, North Hudson Hospital, Weehawken, and the Hasbrouck Heights (N. J.) Hospital; died in the Holy Name Hospital Dec. 15, aged 58.

Feinblatt, Henry M., Brooklyn; Long Island College Hospital, Brooklyn, 1913; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; veteran of World War I; served on the faculty of his alma mater; for many years associated with Kings County Hospital; author of "Clinical Laboratory Medicine" and "Transfusion of Blood"; died Dec. 24, aged 68.

Ferguson, William George, Niagara Falls, N. Y.; University of Western Ontario Faculty of Medicine, London, Ont., Canada, 1924; since 1930 director of the Child Guidance Clinic of the Martha H. Beeman Foundation; served with the Canadian Expeditionary Force in France during World War I; associated with the Mount St. Mary's Hospital and the Memorial Hospital, where he died Dec. 9, aged 60.

Fieramosca, Ettore Francesco Ⓢ Staten Island N. Y.; Loyola University School of Medicine, Chicago, 1933; on the staff of the Staten Island Hospital; died Dec. 31, aged 54.

Gager, Leslie Tracy Ⓢ Washington, D. C.; Johns Hopkins University School of Medicine, Baltimore, 1918; served on the faculty of George Washington University School of Medicine and Howard University College of Medicine; past-president of the Washington Pathological Society; veteran of World Wars I and II; retired from the U. S. Veterans Administration in June, 1953; on the staffs of the George Washington and Garfield hospitals; died Dec. 25, aged 69.

Gardiner, Sheridan Ellsworth, Mount Pleasant, Mich.; Jefferson Medical College of Philadelphia, 1893; served as health officer of Mount Pleasant; died Nov. 20, aged 94.

Gokey, Harold Lewis Ⓢ Alexandria Bay, N. Y.; McGill University Faculty of Medicine, Montreal, Que. Canada, 1917; past-president of the Jefferson County Medical Society; formerly mayor of Alexandria Bay; veteran of World War I; died in the House of the Good Samaritan, Watertown, Dec. 17, aged 66.

Grant, Richard S. Ⓢ Chicago; Meharry Medical College, Nashville, Tenn., 1904; died Dec. 31, aged 81.

Grieco, John Vincent, New York City; Universita di Napoli Facolta di Medicina e Chirurgia, Italy, 1921; died Dec. 13, aged 63.

Groenlung, Wilho Arvid, Vancouver, Wash.; Northwestern University Medical School, Chicago, 1909; died Dec. 10, aged 87.

Gudenkauf, Henry Joseph, Minster, Ohio; Ohio Medical University, Columbus, 1907; formerly member of the county board of health; died in St. Rita's Hospital, Lima, Dec. 20, aged 84.

Hamilton, Guy W. Ⓢ Monrovia, Calif.; University of Louisville (Ky.) Medical Department, 1899; for many years a medical missionary in China; formerly associated with the Madison (Ind.) State Hospital; died Nov. 24, aged 85.

Hertel, Alphons Joseph Ⓢ Whitefish Bay, Wis New York Homeopathic Medical College an Flower Hospital, New York City, 1915; vetera of World War I; on the staffs of St. Joseph's Ho pital and St. Mary's Hospital, Milwaukee, whe he died Nov. 30, aged 68.

Hiestand, Harley Judson Ⓢ Pennville, Ind.; India Medical College, School of Medicine of Purd University, Indianapolis, 1906; served as preside of the Pennville State Bank; died Dec. 23, aged 7

Hohman, Roy Max Ⓢ Chicago; Rush Medical Co lege, Chicago, 1931; member of the Americ Academy of General Practice; veteran of Wor War II; staff member of the Evangelical Hospit died Dec. 23, aged 53.

Holmes, James Ⓢ Springfield, Mass.; University Maryland School of Medicine, College of Physicia and Surgeons, Baltimore, 1917; veteran of Wor War I; associated with the Springfield Hospit where he died Dec. 21, aged 74.

Houser, John Francois Ⓢ Versailles, Ohio; Unive sity of Louisville (Ky.) School of Medicine, 194 interned at the Miami Valley Hospital in Dayto member of the American Academy of Gener Practice; captain in the medical corps of the Arm of the United States from July 5, 1946, to May 2 1948; member of the staff of Wayne Hospit Greenville, Ohio; died Dec. 22, aged 39.

Hynes, John Eldon Ⓢ Minneapolis; University Minnesota Medical School, Minneapolis, 190 member of the American Academy of Gener Practice; past-president of the Minnesota Academ of Medicine; died Dec. 16, aged 81.

Jaudon, George Robert, Lanett, Ala.; Medical Co lege of Alabama, Birmingham, 1951; interned the Jefferson–Hillman Hospital in Birmingham served a residency at the Lloyd Noland Hospit in Fairfield; died in the George H. Lanier Memori Hospital, Langdale, Nov. 22, aged 40.

Karbach, Hylmar E. Ⓢ New Braunfels, Texas; Un versity of Texas College of Medicine, Galveston 1924; member of the American Academy of Genera Practice; veteran of World Wars I and II; on th staff of the New Braunfels Hospital, where he die Dec. 6, aged 60.

Lee, James Grant Ⓢ Bonner Springs, Kan.; Kansa City (Mo.) Medical College, 1892; died in th Bethany Hospital, Kansas City, Dec. 20, aged 91

Lindsay, John William Ⓢ Conway, Mo.; St. Loui University School of Medicine, 1905; died in th Baptist Hospital, Springfield, Dec. 15, aged 84.

Linsky, Harold Ⓢ Kew Gardens, N. Y.; Columbi University College of Physicians and Surgeons New York City, 1922; fellow of the American Col lege of Surgeons; associated with the Terrace Heights Hospital in Hollis, where he died Dec. 28, aged 60.

Lippman, Richard William, Beverly Hills, Calif.; Columbia University College of Physicians and Surgeons, New York City, 1940; interned at the Beth Israel Hospital in New York City; veteran of World War II; one of the founders of the National Nephrosis Foundation; died in Los Angeles Dec. 26, aged 43.

Loeb, Leo Ⓜ St. Louis; born in Mayen, Germany, Sept. 21, 1869; Universität Zurich Medizinische Fakultät, Switzerland, 1898; emeritus professor of pathology at Washington University School of Medicine, where he joined the faculty in 1915 as professor of comparative pathology and later retired as Edward Mallinckrodt professor of pathology; served at McGill University, the University of Illinois, New York State Pathological Laboratory, Buffalo, and the University of Pennsylvania; from 1910 to 1912 secretary of the Section on Pathology and Physiology, American Medical Association; in 1935 received the John Phillips Memorial Medal of the American College of Physicians; in 1942 the St. Louis Medical Society presented him with its award of merit and gold medal; past-president of the Society of Cancer Research; member of the Association of American Physicians, the Endocrine Society, American Association of Pathologists and Bacteriologists, of which he was past-president, and the American Socitey for Experimental Pathology; in 1936 the Mu Chapter of the Phi Beta Pi Medical Fraternity established a lectureship in his honor; served as director of the department of pathology at the Barnard Free Skin and Cancer Hospital; in December, 1950, the American Medical Association honored him by devoting an issue of *Archives of Pathology* to him; author of "Basis of Individuality"; his research included, among other subjects, tissue and tumor growth, physiology of generative organs, pathology and circulation, venom of Heloderna, and analysis of experimental amebocyte tissue; died Dec. 28, aged 90.

Lowe, David Earl Ⓜ Uniontown, Pa.; Jefferson Medical College of Philadelphia, 1912; veteran of World War I; associated with the Uniontown Hospital; died Dec. 19, aged 72.

McCarthy, William Daniel Ⓜ Brooklyn; Queen's University Faculty of Medicine, Kingston, Ont. Canada, 1930; died Dec. 28, aged 53.

McNeill, Willard Payne Ⓜ Spencerville, Md.; College of Medical Evangelists, Loma Linda and Los Angeles, 1935; interned at the Maryland General Hospital in Baltimore; served a residency at the Sibley Memorial Hospital in Washington, D. C., and the Bryn Mawr (Pa.) Hospital; certified by the National Board of Medical Examiners; served on the staff of the Washington Sanitarium and Hospital in Takoma Park, where he died Dec. 28, aged 49.

Mackenzie, Wellie Smith, Adrian, Mich.; Rush Medical College, Chicago, 1905; veteran of the Spanish-American War; served as health officer; associated with the Bixby Hospital; died in Clearwater, Fla., Nov. 19, aged 80.

Main, Roscoe Conkling, Santa Barbara, Calif.; Rush Medical College, Chicago, 1911; formerly health officer of Santa Barbara County; served as health officer of the city of Marquette, Mich.; died Nov. 28, aged 77.

Malik, Nur Muhammad Ⓜ Detroit; University of Michigan Medical School, Ann Arbor, 1927; died Dec. 2, aged 63.

Merica, Forrest Wayne Ⓜ Lakewood, Ohio; Indiana University School of Medicine, Indianapolis, 1925; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Laryngological, Rhinological and Otological Society, and the American Broncho-Esophagological Association; fellow of the American College of Surgeons; associated with the Lakewood (Ohio) Hospital and the Fairview Park Hospital in Cleveland; died in the Lakewood Hospital Dec. 2, aged 58.

Meyer, Maximilian, New York City; Friedrich-Alexanders Universität Medizinische Fakultät, Erlangen, Bavaria, Germany, 1917; died Nov. 13, aged 71.

Miller, Eunice Wilson, Hazel, Ky.; University of Louisville Medical Department, 1910; died Dec. 9, aged 77.

Miller, James Ⓜ Corning, Ohio; Georgetown University School of Medicine, Washington, D. C., 1899; president of the Corning Board of Education; a director of the Perry County Health Department; member of the board of directors of the Corning Bank; died in the Bethesda Hospital, Zanesville, Dec. 18, aged 85.

Moe, George Ⓜ Berkeley, Ill.; Chicago Homeopathic Medical College, 1893; died in the Memorial Hospital of Du Page County in Elmhurst Oct. 29, aged 97.

Morrall, Ralph Richard Ⓜ Youngstown, Ohio; University of Michigan Medical School, Ann Arbor, 1911; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; veteran of World War I; associated with the Youngstown Hospital, where he died in the Southside Unit Dec. 21, aged 71.

Morrison, Lindsey Ⓜ Hammond, Ind.; Hospital College of Medicine, Louisville, 1900; for a time postmaster in West Point, Ky.; veteran of World War I; past-president of the American College of Proctology; served as president of the staff, St. Margaret Hospital; died Dec. 18, aged 89.

Morroway, James Henry Ⓜ St. Joseph, Mo.; Creighton University School of Medicine, Omaha, 1900; member of the American Psychiatric Association; past-president of the Harrison County Medical Society; for many years on the staff of the State Hospital Number 2; died in the Mercy Hospital, Marshalltown, Iowa, Dec. 12, aged 80.

Mulholland, William James Ⓜ Chicago; University of Illinois College of Medicine, Chicago, 1916; veteran of World War I; on the staff of St. Bernard Hospital; died in the South Shore Hospital Dec. 22, aged 72.

Nark, Pius Anthony Ⓜ Minersville, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1936; veteran of World War II; on the staff of the Pottsville (Pa.) Hospital; died Dec. 18, aged 50.

Nerseth, Marvin Ⓜ Klamath Falls, Ore.; University of Nebraska College of Medicine, Omaha, 1931; veteran of World War II; on the staffs of the Hillside and Klamath Valley hospitals; died in the Hillside Hospital Dec. 24, aged 53.

Nosik, William Andre Ⓜ Cleveland; born in Milwaukee May 18, 1911; University of Wisconsin Medical School, Madison, 1935; specialist certified by the American Board of Neurological Surgery; member of the Harvey Cushing Society, Association for Research in Nervous and Mental Diseases, and the Central Neuropsychiatric Association; fellow of the American College of Surgeons; past-president of the Cleveland Society of Neurology and Psychiatry and Ohio State Neurological Society; veteran of World War II; associated with St. Luke's, St. Vincent's Charity, Huron Road, Glenville, Doctors, and Lakeside hospitals; in 1955-1956 editor of the *Bulletin of the Cleveland Academy of Medicine;* died Dec. 6, aged 48.

O'Donnell, Albert Thomas Ⓜ Port Orchard, Wash.; Creighton University School of Medicine, Omaha, 1952; veteran of World War II; died in Bremerton Dec. 23, aged 42.

Osborn, Dean Hill, Klamath Falls, Ore.; State University of Iowa College of Medicine, Iowa City, 1910; veteran of World War I; associated with the Klamath Valley Hospital and the Hillside Hospital, where he died Dec. 25, aged 74.

Perlman, Samuel Ⓜ Carthage, Texas; Indiana University School of Medicine, Indianapolis, 1930; member of the American Academy of General Practice; member and past-president of the staff of the Panola General Hospital; died Dec. 22, aged 57.

Pelant, Francis Joseph, Newton, Ill.; Chicago College of Medicine and Surgery, 1914; died in St. Anthony Memorial Hospital, Effingham, Dec. 5, aged 73.

Picozzi, John Avand Ⓜ Providence, R. I.; Tufts College Medical School, Boston, 1922; formerly county medical examiner; served on the staff of the Veterans Administration Hospital, where he died Dec. 3, aged 61.

Prior, James Howland Ⓜ Cranston, R. I.; Hahnemann Medical College and Hospital of Philadelphia, 1902; specialist certified by the American Board of Internal Medicine; served on the state board of health and the state board of medical examiners; formerly on the staff of the Rogers Williams General Hospital in Providence, where in 1953 the nurses' home was named Prior Hall in his honor; died Dec. 23, aged 81.

Proxmire, Theodore Stanley Ⓜ Lake Forest, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1904; veteran of World War I; served as president of the Lake County Tuberculosis Association; fellow of the American College of Surgeons; a founder and for many years president of the Lake County Tuberculosis Sanatorium, Waukegan; on the staffs of St. Therese Hospital in Waukegan and the Lake Forest Hospital; for many years director of the Allendale School for Boys, Lake Villa; died Dec. 16, aged 77.

Rattunde, Henry Frederick, Duarte, Calif.; University of Wisconsin Medical School, Madison, 1949; interned at the Broadlawns Polk County Hospital in Des Moines, Iowa, where he served a residency; served a residency at the Iowa Methodist Hospital in Des Moines; associated with the City of Hope; spent two years in the Air Force; died Nov. 28, aged 35.

Regner, Mathias Frederick Ⓜ Colonel, U. S. Air Force, New York City; born in West Bend, Wis., Dec. 16, 1912; University of Wisconsin Medical School, Madison, 1937; veteran of World War II; received the Bronze Star Medal, European Theater of Operations Medal, American Defense Service Medal, German Occupation Medal, Army Accommodation Medal, National Defense Service Medal, World War II Victory Medal, and the Air Force Longevity Service Award with four bronze Oak Leaf Clusters; released from active military service February, 1946, and entered the Army Reserve Corps and private practice; returned to active military service March 11, 1949, and his duties included surgeon of the 311th Air Division at Topeka, Kan., surgeon 93d Bomb Wing, Castle AFB, Calif., surgeon 6th Air Division, MacDill AFB, Fla., chief of professional services, and wing and base flight surgeon; his last assignment in the Zone of Interior (U. S.) was hospital commander and division surgeon at the 380th TAC Hospital, Plattsburgh, N. Y., at which time he was reassigned to Germany and to the 7112th Central Medical Group, Wiesbaden Air Base, Wiesbaden, Germany, where he assumed command on July 15, 1959; promoted to the grade of colonel April 15, 1953; specialist certified by the American Board of Preventive Medicine; member of the American Academy of General Practice and the Aero Medical Association; died at Wiesbaden, Germany, Nov. 20, aged 46.

Ressa, Daniel Arcangelo, Pittsburgh; Fordham University School of Medicine, New York City, 1916; served on the staffs of St. John's and St. Joseph's hospitals; died in the Shadyside Hospital Dec. 16, aged 72.

Roach, Fulton R., Queen City, Texas; (licensed in Texas by years of practice); died Dec. 6, aged 83.

Robbins, Bernard S., New York City; University of Cincinnati College of Medicine, 1929; specialist certified by the American Board of Psychiatry and Neurology; fellow of the American Psychiatric Association; clinical professor of psychiatry at the New York University College of Medicine; on the staff of Flower and Fifth Avenue Hospitals; died Dec. 16, aged 54.

Robins, Bernard Leo, Glendive, Mont.; University and Bellevue Hospital Medical College, New York City, 1915; died Dec. 28, aged 66.

Rogers, James Dudley Ⓜ Wyandotte, Mich.; University of Western Ontario Faculty of Medicine, London, Ont., Canada, 1931; associated with the Wyandotte General Hospital, where he died Nov. 30, aged 53.

Roller, William Crawford, Mint Spring, Va.; University of Virginia School of Medicine, Charlottesville, 1899; died in Staunton Nov. 23, aged 83.

Rosenberg, Theodore Ⓜ New York City; Rush Medical College, Chicago, 1932; veteran of World War II; interned at the Michael Reese Hospital in Chicago; director of medical care of the department of welfare; died Dec. 28, aged 54.

Roy, Bert William Ⓜ Sussex, N. J.; Albany (N. Y.) Medical College 1908; past-president of the Sussex County Medical Society; died Nov. 17, aged 81.

Rundlett, Emilie Viett Ⓜ Jersey City, N. J.; Medical College of South Carolina, Charleston, 1901; served on the faculty of Seton Hall College of Medicine and Dentistry; fellow of the American College of Physicians; associated with the isolation facilities of the Medical Center of Jersey City, where she died Nov. 17, aged 83.

Russell, Ralph Swisher Ⓜ San Diego, Calif.; University of Nebraska College of Medicine, Omaha, 1925; fellow of the American College of Surgeons; associated with the Paradise Valley Sanatorium and Hospital, National City, Scripps Memorial Hospital, La Jolla, and Children's Hospital and Quintard Hospital in San Diego; consulting obstetrician and gynecologist, La Mesa Community Hospital in Coronado; veteran of World War I; died in the Scripps Memorial Hospital, La Jolla, Dec. 10, aged 59.

Schumacher, Nicholai A., St. Johns Station, Mo.; St. Louis College of Physicians and Surgeons, 1906; died Nov. 6, aged 74.

Scull, Ralph Horace Ⓜ Chicago; Rush Medical College, Chicago, 1929; specialist certified by the American Board of Dermatology; member of the American Academy of Dermatology and Syphilology; served on the faculty of his alma mater; died Dec. 16, aged 61.

Shafer, Irving Everett Ⓜ Salisbury, N. C.; North Carolina Medical College, Charlotte, 1914; past-president of the Rowan-Davie Counties Medical Society; member of the American Academy of General Practice; served as a member of the county board of health; veteran of World War I; associated with the Rowan Memorial Hospital; died Dec. 6, aged 71.

Shaw, Christopher Campbell Ⓜ Captain, U. S. Navy, Philadelphia; born in Chichester, N. Y., June 12, 1901; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1931; specialist certified by the American Board of Internal Medicine and the American Board of Preventive Medicine; certified by the National Board of Medical Examiners; member of the American College of Cardiology and the Aero Medical Association; fellow of the American College of Physicians, of which he was educational director; captain in the medical corps of the U. S. Naval Reserve from 1941 to 1945; since 1948 captain in the medical corps of the U. S. Navy; during World War II a flight surgeon aboard the aircraft carrier escort Solomons; senior medical officer in charge of industrial medicine at the Philadelphia Naval Base; on the faculty of Hahnemann Medical College; formerly director of the research division for the Bureau of Medicine and Surgery in the U. S. Navy; at one time medical director of the medical research laboratory for Sharp & Dohme Inc.; in 1954 the Association of Military Surgeons awarded him the Sir Henry Wellcome medal and prize and in 1950 the Louis Livingston Seaman prize; died in the U. S. Naval Hospital Dec. 5, aged 58.

Shevitz, David Mattus Ⓜ Hackettstown, N. J.; Medical College of Virginia, Richmond, 1929; on the staffs of the Newton (N. J.) Memorial Hospital and the Morristown (N. J.) Memorial Hospital, where he died Dec. 3, aged 53.

Showak, George Ⓜ Saxonburg, Pa.; Temple University School of Medicine, Philadelphia, 1956; interned at the Naval Hospital in Philadelphia, where he served a residency; served in the regular Navy; died Dec. 17, aged 31.

Silsby, Harry Zettlemeyer Ⓜ Sanford, Fla.; Louisiana State University School of Medicine, New Orleans, 1936; veteran of World War II and received the Bronze Star in the Pacific Theater; died Dec. 22, aged 58.

Simonton, Richard Deweese Ⓜ Boise, Idaho; University of Oregon Medical School, Portland, 1930; in 1946 member of the House of Delegates of the American Medical Association; since 1957 councilor of the Idaho State Medical Association; fellow of the American College of Surgeons, of which he was a charter member, and in 1955 president of its Boise Valley chapter; died in St. Luke's Hospital Dec. 6, aged 54.

Simpson, Henry Hardy Ⓜ Elon College, N. C.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1925; member of the American Academy of General Practice; died in the Baptist Hospital, Winston-Salem, Dec. 19, aged 62.

Sirmons, Derrel Chatfield Ⓜ Dahlonega, Ga.; Medical College of Georgia, Augusta, 1943; interned at the Macon Hospital in Macon, where he served a residency; died Dec. 5, aged 44.

Skirball, Louis Irving Ⓜ Boston; University of Vermont College of Medicine, Burlington, 1913; fellow of the American Academy of Pediatrics; for many years a medical consultant of the rehabilitation department of the Veterans Administration; died Nov. 25, aged 69.

Smith, Augustus Kenly Ⓜ Logan, Ohio; Medical College of Ohio, Cincinnati, 1889; died in the Hocking Valley Hospital Dec. 2, aged 92.

Smith, Robert Lee Ⓜ Pomona, Calif.; University of Nashville (Tenn.) Medical Department, 1902; member of the staff of the Pomona Valley Community Hospital; two terms president of the Pomona Branch of the Los Angeles County Medical Association; died Dec. 9, aged 85.

Smith, Robert Wilhoyte Ⓜ Owensboro, Ky.; Vanderbilt University School of Medicine, Nashville, Tenn., 1938; interned at the Columbia Hospital in Milwaukee, where he served a residency; served a residency at the Milwaukee Children's Hospital; past-president of the Daviess County Medical Society; member of the Southeastern Surgical Congress; veteran of World War II; died Dec. 16, aged 45.

Summers, J. Dent Ⓜ Hickory, N. C.; University of Pennsylvania School of Medicine, Philadelphia, 1939; interned at the George F. Geisinger Memorial Hospital in Danville, where he served a residency; served a fellowship in surgery at the Cleveland Clinic Foundation Hospital in Cleveland; fellow of the American College of Surgeons; veteran of World War II; on the staff, Richard Baker Hospital; died Nov. 23, aged 46.

Swango, William Ray Ⓜ Ironton, Ohio; Tulane University School of Medicine, New Orleans, 1937; veteran of World War II; died in the Lawrence County General Hospital Dec. 5, aged 52.

Thomas, George Norfleet Ⓜ Vineland, N. J.; Jefferson Medical College of Philadelphia, 1923; fellow of the International College of Surgeons; past-president of the Cumberland County Medical Society; veteran of World War I; associated with the Newcomb Hospital; died Dec. 2, aged 63.

Thomison, Harry Elijah Ⓜ Upper Montclair, N. J.; Jefferson Medical College of Philadelphia, 1918; served on the staff of the St. Barnabas Medical Center in Newark; died Dec. 15, aged 64.

Wallace, Lew Edwin, Seymour, Ind.; Medical College of Indiana, Indianapolis, 1902; died in the Jackson County Hospital Nov. 25, aged 82.

Westphaelinger, Henry Frederick Ⓜ St. Louis; St. Louis University School of Medicine, 1919; for many years associated with the Veterans Administration Hospital; died in the Deaconess Hospital Dec. 8, aged 64.

Wetmore, William Olendorf Ⓜ Major, U. S. Army, retired, St. Petersburg, Fla.; George Washington University School of Medicine, Washington, D. C., 1895; retired from the U. S. Army in December, 1933; veteran of World War I; served on the faculty of his alma mater; died Nov. 28, aged 85.

Willett, Robert Herman Ⓜ Jonesboro, Ark.; University of Louisville (Ky.) Medical Department, 1910; on the staff of St. Bernard's Hospital, where he died Dec. 2, aged 78.

Williams, John H., Louisville, Ky.; Meharry Medical College, Nashville, Tenn., 1902; veteran of the Spanish-American War and World War I; died Nov. 29, aged 80.

Wofford, Helen Dyson Ⓜ Johnson City, Tenn.; University of Pennsylvania School of Medicine, Philadelphia, 1928; on the staff of the Jones Eye, Ear, Nose and Throat Hospital; died in the Holston Valley Community Hospital, Kingsport, Dec. 2, aged 52.

Womeldorf, John M., Glendale, Calif.; Rush Medical College, Chicago, 1897; died Nov. 30, aged 90.

FOREIGN LETTERS

DENMARK

Radioactive Gold for Cancer.—Hanson and Haug (*Ugesk. laeger*, Oct. 22, 1959) used radiogold in the treatment of 56 patients who had carcinomatous effusions into the pleural and peritoneal cavities. The injection into these cavities was made at the time of the aspiration of the effusion, some of which was left in place to facilitate the spread of the injected solution. The site of the original tumor was in most cases the breast or ovary. Because of the advanced stage of the disease when this treatment was started, 48 of the 56 were dead at the conclusion of this study, yet it was concluded that in about 28 of these patients a good palliative effect was achieved and that in another 11 or 12 there was moderate relief. Better results might have been obtained by repeating this treatment several times. It might also be used as a prophylactic measure directly after surgical treatment. Primary tumors of the pleura with effusion might also respond well to this treatment, which in this series provoked no serious side-effects.

Potency After Prostatectomy.—Dr. V. Hvidt (*Nord. Med.*, Nov. 19, 1959) investigated the influence of prostatectomy on potency. The literature on the subject betrays great variations in the findings of different observers. In his series of 211 there were 126 with postoperative retention of potency, but 11% of those under the age of 60 years had become impotent. While 182 had had retropubic prostatectomy, 29 had had the transvesical operation. A comparison of their postoperative sexual functions suggested that the retropubic operation was the more likely to cause impotence. For comparatively young candidates for prostatectomy it might therefore be well to let the choice of operation depend to some extent on the likelihood of its interference with sexual functions.

Simulation of Malignant Disease by Miliary Tuberculosis.—Dr. B. Zachau-Christiansen (*Ugesk. laeger*, Nov. 5, 1959) stated that it was difficult to diagnose miliary tuberculosis in spite of the many tests for it available in a modern hospital. His three women patients were aged, respectively, 40, 73, and 65 years. Pulmonary tuberculosis was suspected in the first, but x-ray and clinical findings pointed to carcinosis, and it was not until after her death that tubercle bacilli were found in the stomach contents. The diagnosis of tuberculosis was confirmed post mortem. In the second patient no tubercle bacilli could be found in the sputum, and the x-rays were suggestive of pulmonary metastases. The macroscopic findings post mortem were suggestive of but not unequivocally indicative of tuberculosis, and it remained for the microscopic examination to give the correct diagnosis. Even then no tubercle bacilli were found. The third patient had no previous record of tuberculosis, but she had been operated on for cancer of the thyroid four years earlier. A pleural effusion yielded neither cancer cells nor tubercle bacilli. She died after an attack of pneumonia. The macroscopic postmortem findings indicated carcinosis of the lungs, pleura, peritoneum, liver, and regional lymphatic nodes, but the microscopic findings reversed the diagnosis in favor of tuberculosis. In view of these cases it may be wise to give antituberculous treatment even when there is only a suspicion of this disease.

GERMANY

Lymphocyte Systems.—E. Grundmann of Freiburg (*Klin. Wchnschr.* 37:66, 1959) said that two types of lymphocyte which are different in genesis and structure may be distinguished in man, as in the rat. A macronucleolar form develops exclusively in the follicles, and a multinucleolar form develops, usually in the sinuses of spleen and lymph nodes. Both types of cells are easily shown by phase contrast in crush preparations, but they are also easily identified in smears from peripheral blood after modified methylene blue staining. In the blood smears from 15 healthy adults it was found that about 72% of the lymphocytes were of the follicular type and 28% of the sinus type. In children before puberty this proportion was 79:21.

Prevention of Kernicterus.—Linneweh and Bickel of Marburg (*Klin. Wchnschr.* 37:963, 1959) stated that the bilirubin encephalopathy of premature infants, which causes permanent cerebral damage or death from kernicterus, may be prevented by timely exchange transfusion. Physicians do not agree about when this therapy should be instituted. A critical bilirubin level of about 20 mg. per 100 ml. is not a suitable indication because kernicterus sometimes occurs even at bilirubin blood concentrations below 15 mg. per 100 ml. and sometimes fails to occur at concentrations above 30 mg. per 100 ml. The bilirubin blood level is only one of several factors that influence the development of kernicterus. The need for exchange transfusion was considered imperative

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The items in these letters are contributed by regular correspondents in the various foreign countries.

mainly when prodromal symptoms appeared. Reexamination showed that 15 children 1½ to 3¼ years of age who were subjected to exchange transfusion after purely clinical indications developed normally and 16 premature infants with hyperbilinuremia of 21 to 32 mg. per 100 ml. remained without clinical symptoms although no exchange transfusion was performed. They too had developed normally up to the age of 1½ to 3¼ years.

The authors concluded that one may await the appearance of prodromal symptoms of bilirubin encephalopathy in premature infants with hyperbilirubinemia before resorting to exchange transfusion because these symptoms are entirely reversible and do not endanger the later development of the children. The prodromal symptoms include feeding difficulties, severe loss of weight, variations in temperature, restlessness, excessive yawning, and dulness. In absence of such clinical indications, exchange transfusion is unnecessary and should be avoided because of the risk involved.

Wound Treatment.—H. Krieger of Düsseldorf (*Medizinische,* pp. 1172-1174, 1959) stated that a new wound cover, a cross-woven dense foil, permeable to humidity and air, which consists of 77% cellulose, 7.8% water, 15% glycerin and glycol, and 0.2% copper, has proved valuable. It is applied dry to aseptic wounds. For septic wounds it may be covered with moist muslin or applied dry; for superficial wounds it is applied over a thin layer of ointment or zinc muslin; and for dermatological wounds, eczema, etc., it is moistened.

Prednisolone for Multiple Sclerosis.—Schrader and Schild of Marburg (*Klin Wchnschr.* 37:946, 1959) said that prednisolone should be tried in all patients with acute or subacute multiple sclerosis. The improvement of hitherto refractory symptoms, in some patients noticeable after the first day of this treatment, proves that the treatment is effective. In patients with chronic or slowly progressing multiple sclerosis, however, even prednisolone will usually not induce any improvement. The use of prednisolone is definitely indicated for patients in whom the disease appears for the first time and for patients with fresh progressions, especially when there is fresh involvement of the optic nerve. Therapy should be intensive. Large doses should be given intermittently. More than one course of the drug should be administered, but in chronically progressive cases this is advisable only if the first course caused a noticeable improvement.

Effects of Low Cardiopulmonary Minute Volumes.—G. Schönbach and co-workers of Giessen (*Thoraxchirurgie,* p. 516, 1959) studied the behavior of various organs during and after artificial perfusion with different minute volumes of blood in 42 experiments on animals. Nine dogs were given perfusions for 25 to 60 minutes with 20 to 35 cc. of blood per minute per kilogram of body weight. When the low-flow principle was used, the arterial blood pressure fell to about 25 mm. Hg. After 45 minutes of perfusion the blood pressure could be raised for only a brief period by increasing the minute volume. The body temperature fell regularly, in some animals by 4 C (7.2 F), although the blood was warmed during extracorporeal circulation. Acidosis occurred shortly after the artificial perfusion was started, and after 45 minutes this acidosis could not be corrected by increasing the minute volume. Albumen was repeatedly found in urine samples taken after perfusion, especially when perfusion lasted for more than 30 minutes.

In four animals pulmonary edema was found on histological examination. A granular destruction of the myocardial fibers was noted in the heart, especially on the left side, and also in the cellular protoplasm of the liver. Protein bodies and erythrocytes were found in Bowman's capsules and the renal tubules as well as in the interstitial tissues. The adrenal bodies showed severe lipoid degeneration in contrast to the findings in animals given perfusion with a normal minute volume. The epithelial cells of the thyroid gland became very active, which is an alarm reaction. Microscopic examination revealed contraction of arterioles and reduced speed of flow when the minute volume was reduced to about 65 cc. per kilogram, and when it was reduced to 40 cc. per kilogram the flow became sluggish and some of the capillary areas appeared cut off. On further reduction of the minute volume there was only minimal perfusion in the small arteries and arterioles and the capillary blood stream was disrupted almost completely. These studies showed that, with use of the small minute perfusion volumes of the low-flow principle, hypoxemia of the tissues leads to changes in organic structure which may be reversible or irreversible, depending on their severity.

Osteoarthritis of the Knee.—H. Leonhard (*München med. Wchnschr.* **101**:974-975, 1959) stated that the chief problem connected with osteoarthritis of the knee is the recurrence of symptoms when treatment is discontinued. A series of about 50 patients remained free of symptoms or were at least essentially improved for several years after being treated the following way: the knee joint was punctured at the upper out margin, effusions were evacuated, 1 cc. (25 mg.) of desoxycorticosterone acetate suspension was instilled, and the joint was actively and passively exercised and then covered with an ichthyol dressing. This dressing was left in place for one to three weeks. It may be necessary to repeat this treatment once or twice, and it may also be repeated in a relapse. When the condition is one of true osteoarthritis, no contraindications are apparent.

Radiation Sickness.—Schubert and Maass of Hamburg University (*Deutsche med. Wchnschr.* 84:1130-1133, 1959) stated that the era of A-bomb tests has caused men to search for chemical protection against exposure to ionizing radiations. No known substance provides protection if it is given after irradiation. Some substances, however, reduce the body's sensitivity to irradiation if they are applied prior to exposure. Such protective substances include sodium cyanide, which is too toxic for practical use, and cysteine. The effect of cysteine is due to its sulfhydryl (SH) group which reactivates enzymes, the SH groups of which were oxidized by the irradiation insult. Cystin, the disulfide form of cysteine, is ineffective as it has no free SH group. Other effective substances are cysteamine, cystamine, and serotonin. The various protective substances do not counteract irradiation reactions to the same degree. It may be that early reactions, such as a steep drop in the leukocyte count, loss of weight, and inhibition of desoxyribonucleic acid are not modified but that recovery is accelerated when the protectors have been given before. Late reactions, however, such as changes of cell structure and of the composition of the blood proteins are reduced by administration of cysteine. The substance also protects reproductive ability and embryonal development but does not effect the rate of mutation induced by radiation.

Chlorpromazine in the Treatment of Cancer.—At the first International Symposium on Chemotherapy, in Geneva, in September, Prof. W. Lührs of Berlin reported surprising results with chlorpromazine in the treatment of malignant tumors. The tumor cells, which proliferate at a high rate, are in a state of relative energy deficiency, since the rapid growth demands multiple high synthetic performances which involve a high energy consumption and these cells have reduced efficiency because of their characteristic metabolism, which is different from that of other cells. Energy released on the oxidation of substrate hydrogen is used mainly for the synthesis of high-energy phosphate compounds, such as adenosine triphosphate. Cell respiration and construction of high-energy phosphates are therefore connected in the fundamental process of oxidative phosphorylation. Only the energy released when high-energy phosphates are split up is available for the anabolism of the cell.

It was thought possible to deprive the malignant tumor which works with increased energy requirements but decreased energy supplies by disconnecting the construction of high-energy phosphate from the process of cell respiration in oxidative phosphorylation of biologically utilizable energy enough to impair the vitality of the tumor. According to this hypothesis, the tumor cell would then more easily succumb to the body's defenses and to cytostatic substances and ionizing rays. While previous antimitotic treatments were mainly based on the difference in proliferation rates between normal and malignant cells, the decoupler principle makes use of the different energy requirements of normal and malignant cells, and when this principle is applied the uneconomical metabolism of tumor cells probably is a further factor which promotes therapy.

In vitro tests showed that high concentrations of chlorpromazine acted as a potent decoupler of oxidative phosphorylation. The effect on tumor mitochondriae was more marked than that on mitochondriae of normal cells. The drug does not stimulate the respiration of isolated mitochondriase. Low concentrations of chlorpromazine, on the other hand, may promote oxidative phosphorylation. Only high concentrations have the decoupler effect. Chlorpromazine in suitable concentration retarded the growth of tumors in the animal experiments. The first clinical trials of chlorpromazine showed its effectiveness as a sensitizer of the tumor cell to cytostatic substances and high-energy rays also in the treatment of malignant tumors. Chlorpromazine, 400 mg. given daily by mouth for several months, with cytostatic or x-ray treatment or hormones, effected impressive remissions. The large doses of chlorpromazine were surprisingly well tolerated.

Nucleic Acid Content in Tumor Tissue.—Bürger and Wüst of Leipzig University (*München med. Wchnschr.* [no. 44] 101:1941, 1959) studied the nucleic acid content of cancer tissue and matrix and compared it with that of normal tissue. Normal tissues were found to have various nucleic acid levels, specific for each type of tissue. On the other hand, malignant tumors and their metastases had an almost uniform nucleic acid content in spite of the multiplicity of biological and morphologic differences. The average content of desoxyribonucleic acid and ribonucleic acid was almost the same in bronchial carcinoma, gastric carcinoma, colonic carcinoma, carcinoma of the uterus, and their metastases. Tumors originating from interstitial tissue did not differ from epithelial neoplasms in their biochemistry.

In patients with chronic leukemia the liver had a significantly higher desoxyribonucleic acid content than the homologous normal organ. There were marked differences in ribonucleic acid content and desoxyribonucleic acid content between liver, lung, and lymph node metastases and their matrixes. An interrelationship between histological fine structure and nucleic acid content was also found in the case of bronchial carcinoma. The small-celled bronchial carcinomas, which are considered particularly malignant, had a much higher nucleic acid content than the differentiated tumors of the bronchi. Benign tumors had much lower nucleic acid levels than malignant growths. Increased protein hynthesis is the cause of the high ribonucleic acid content in cancerous growth. The cause of high desoxyribonucleic acid content may be seen in the great number of cells, the high rate of division, and the increase of desoxyribonucleic acid in the cell nucleus.

INDIA

Anemia and Cirrhosis of Liver.—Sengupta and Aikat (*J. Indian M. A.*, vol. 33, Nov. 16, 1959) stated that hepatic cirrhosis is fairly common in India. They studied a series of 53 patients who were not receiving any hematinic treatment. Of these, 38 were found to have orthochromia and 15 hypochromia which was probably due to an iron deficiency. Those with macrocytosis had a less severe degree of anemia than those with other morphologic types. The range of the reticulocyte count varied from 1 to 16%. This count was not related to the type or degree of anemia. Some patients with severe anemia showed anisocytosis and poikilocytosis. Target cells were found in 30 patients. All those with hypochromia had a fair number of target cells in the peripheral blood. Their presence was related to hyperbilirubinemia. Leukopenia was frequently associated with enlargement of the spleen. The only patient with leukocytosis had no such enlargement. Many patients had neutropenia and almost all had lymphopenia. Thrombocytopenia was observed in 32.

Fractional gastric analysis showed that hypochlorhydria was common, but achlorhydria was found in only two. The values for total direct and indirect bilirubin showed no correlation with the degree of anemia or with the different morphologic types of anemia. Increased reticulocyte count was found in 75% of those with normal range of total indirect bilirubin. A high direct-indirect quotient was found to be frequently associated with macrocytic anemia, but it had no relation to the degree of anemia. The fecal urobilinogen content also showed no relation to the degree or type of anemia. Examination of the marrow showed normoblastic hyperplasia with macronormoblasts in 50% of those with macrocytic anemia independent of bleeding. Eleven patients had an increased percentage of basophilic normoblasts, and 16 showed increased late normoblasts. Three patients with macrocytic anemia showed giant metamyelocytes. Increased plasma cells related to hyperglobulinemia were found in many patients. The marrow changes were characterized predominantly by normoblastic hyperplasia. The association of a high direct-indirect quotient with macrocytosis suggested that macrocytosis occurred when the balance in the two types of bilirubin altered.

Of the 53 patients 13 had macrocytic, 2 microcytic, and 38 normocytic anemia. About 12 of those with normocytic anemia showed a tendency to macrocytosis. Only one patient with macrocytosis had a high reticulocyte count, which would account for the macrocytosis only in this single case. Leukopenia and thrombocytopenia were almost uniformly present. All these factors suggest that nutritional factors play an important role in the causation of anemia in patients with cirrhosis. A history of hemorrhage, recent or old, was obtained from only four patients. Anemia with normoblastic marrow, leukopenia, and an enlarged spleen were present in 23 of the patients and could be explained on the basis of hypersplenism. An epinephrine test of 12 patients, however, showed negative results for all. Some improvement occurred in some anemic patients with enlarged spleen after splenectomy. Hypervolemia, which could also lead to anemia, was found in six patients who showed hyperplastic changes in the marrow. The factors that could have been responsible for causing anemia in these patients with cirrhosis were dyshemopoiesis, hemorrhage, hypersplenism, hypervolemia, and hemolysis, each of which might have operated alone or in combination.

Visual Method of Reading the Systolic Blood Pressure.—P. L. Deshmukh (*Current M. Pract.*, vol. 3, Oct., 1959) stated that the visual method is more accurate than the auscultatory method for reading the systolic blood pressure. He often noticed that fluctuations appeared in the mercurial column long before sounds could be heard by auscultation over the brachial artery after gradual deflation of the armcuff. The earliest point where such fluctuations appeared was taken as the systolic reading. A difference of 5 to 30 mm. Hg was often observed between the reading so recorded and that obtained by the usual auscultatory method. This difference was most marked in the group over 40 years of age where evidence of arteriosclerosis was present. As a result of these sclerotic changes, the artery does not readily respond to the systolic input by distension as a healthy vessel would. The difference between the visual and auscultatory readings would give an idea of the extent of the sclerosis.

Post-lumbar-puncture Headache.—G. B. Hanji (*Current M. Pract.*, vol. 3, Oct., 1959) said that one of the major sequelae of spinal anesthesia is post-lumbar-puncture headache, which is often refractory to the usual analgesics. The beneficial effect of dihydroergotamine in these headaches as described by some has no definite pharmacological basis. The author tried this drug in a series of 50 patients with post-lumbar-puncture headache. The anesthetic used in all these patients was dibucaine with 5% dextrose in doses of 1 or 2 cc. The amount of spinal fluid lost during lumbar puncture did not exceed 1 or 2 cc. Identical 22-gauge needles were used in every case. Patients in whom the first puncture was not successful were excluded from the series, as the headache is sometimes attributed to the trauma of the periarachnoid area after repeated tappings.

The prepuncture tension, which was judged by the rate of flow of the cerebrospinal fluid, was almost identical in all. These patients were given 1 cc. (0.2 mg.) of dihydroergotamine intramuscularly. Usually one injection was enough. Only nine received a second injection two hours after the first when symptoms recurred. The headache was moderate or severe. No other drugs were used. Dihydroergotamine was given only a few hours after the headache started, usually in the earlier part of the night in patients operated on in the morning. Some patients also complained of backache. Of the 50 patients 33 showed rapid improvement. The headache disappeared completely or was greatly relieved in about an hour. Of the rest, 11 had slight relief and 6 showed no response. Of the five who complained of backache, none was relieved of this symptom after the injection, although the headache was relieved in two. In nine patients a relapse occurred which invariably responded to a second injection of dihydroergotamine. No untoward side-effects were noted.

Antihypertensive Drugs.—Datey and Joshi (*J. Postgraduate Med.*, vol. 5, Oct., 1959) evaluated the effects of various antihypertensive drugs, alone and in combination, in 53 patients with hypertension. Blood pressure was recorded from both arms. The maximum blood pressure in the series was 230/160 mm. Hg, and the minimum systolic pressure (140 mm. Hg.) was found in a patient with a diastolic pressure of 100 mm. Hg. The lowest diastolic pressure (90 mm. Hg) was recorded in a patient with a systolic pressure of 170 mm. Hg. The antihypertensive drugs used were tablets containing 0.25 mg. of reserpine; Adelphane tablets, a combination of 10 mg. of 1-4 dihydrazino-phthalazine and 0.1 mg. of reserpine; hypotensen tablets each containing 0.3 Gm. of Rauwolfia, 30 mg. of theobromine, and 15 mg. of phenobarbital; 100-mg. tablets of Rauwolfia; 50-mg. tablets of hydralazine; 25-mg. tablets of chlorisondamine; 40-mg. tablets of pentolinium tartrate; injections containing 138 mg. of hexamethonium tartrate; and 10-mg. tablets of mecamylamine hydrochloride.

The same patient was given different drugs at different times. If a drug failed to act, the dosage was increased until side-reactions occurred, at which time another drug was substituted or a combination of drugs was used. The basal blood pressure was determined in most patients before starting the trial by giving 30 mg. of phenobarbital three times a day for 8 to 21 days. Patients with malignant hypertension; those with grade 3 hypertensive retinopathy and severe headache, giddiness, or signs of congestive cardiac failure; and those with cerebrovascular episodes were immediately put on antihypertensive treatment. Thirty-seven patients complained of headache and 35 were giddy when walking or after exertion. Other symptoms included cough with expectoration, palpitation, epistaxis, hemoptysis, precordial pain, dyspnea on exertion, nocturnal dyspnea, and edema of the ankles. Fundoscopy revealed grade 1 retinopathy in 13 patients, grade 2 in 8, grade 3 in 7, grade 4 in 4, arteriosclerotic changes in 7, lenticular opacities in 3, diabetes in 1, and anemia in 1. Only two had normal fundi. Twenty-one had a urea nitrogen level above normal, and the nonprotein nitrogen level was high in 17.

After treatment the headache was improved in 20 of 37 patients as the blood pressure decreased. Only three patients became less giddy. The nonprotein nitrogen level showed a significant decrease after treatment in nine.Ophthalmodynamometry done in 27 patients showed cephalic hypertension in 22 which became lower after treatment in 6. Reserpine lowered the pressure in 16 of 20 patients. Of the four who failed to respond, two had malignant hypertension; three of the four responded to the ganglion-blocking agents. Reserpine helped in maintaining the decreasing pressure after it was brought down by mecamylamine. Hypotensen lowered the pressure in four of five patients and six received this drug after they received reserpine. Five of these responded. Hypotensen caused a greater reduction in the pressure than did reserpine. This could have been due to the different content of reserpine in these preparations, and there might have been some synergism between reserpine and the other constituents of Hypotensen. The contained phenobarbital made some patients extremely drowsy. One patient who did not respond to Hypotensen and had a grade 3 retinopathy also failed to respond to ganglion-blocking agents. Rauwolfia given to seven patients caused some lowering of pressure in all, but normal levels were attained in only five. Three patients developed tolerance to this drug. Postural hypotension to some extent occurred in all patients after the use of Rauwolfia or its derivatives.

This group of drugs did not significantly alter the pressure in patients who had failed to respond to the ganglion-blocking agents. In one patient in whom the pressure was decreased by a ganglion-blocking agent it could be maintained at the lowered level by reserpine. Side-reactions with reserpine and the crude preparation of Rauwolfia were about the same. Adelphane tried in four patients produced a moderately good response, but three developed a tolerance, while side-reactions such as shivering, nausea, and headache occurred if the dosage was increased. Of the three patients who were given both reserpine and Adelphane, the latter produced better results in two. Hydralazine was tried in a few patients. It also produced tolerance in three while the pressure was lowered moderately in one and not at all in two. Hexamethonium lowered the pressure in five. The patients did not respond to other drugs given later. In two pentolinium was substituted for hexamethonium along with reserpine when a temporary fall in pressure was produced. Increasing the dosage of pentolinium produced side-reactions.

As an emergency measure two patients were given reserpine and hexamethonium intramuscularly but only one responded. Mecamylamine was effective in all 10 patients to whom it was given. Postural hypotension occurred in all but one. Although the combined action of more than one antihypertensive drug in any one patient was more effective, in actual practice it was easier to regulate the doses of each of the antihypertensive drugs when they were used separately and not incorporated in one tablet. On the whole the Rauwolfia drugs proved useful in patients with mild and moderate hypertension. Their side-reactions did not necessitate withdrawal of the drug, as the margin of safety is wide. Although they did not help patients who were not improved by ganglion-blocking agents, they could be safely and effectively used to prolong the hypotensive response induced by these drugs when their continuous administration would likely have led to side-effects.

Although tolerance to Rauwolfia does occur, it could be overcome by increasing the dose. When used in combination with other antihypertensive agents, reserpine helps in lowering the dose of the other agent thus reducing the possibility of side-reactions. Chlorisondamine and mecamylamine proved effective in patients who had become refractory to other agents. Results with both were similar, although chlorisondamine was less potent. Partial tolerance developed more quickly and more often with this drug than with mecamylamine. Tolerance was common with Adelphane and side-reactions were same as with Rauwolfia. Hydralazine proved of little use in refractory patients, while side-reactions and partial tolerance were common.

Sulfadiazine Lipid Emulsion.—K. J. Vyas (*J. Indian M. A.*, vol. 33, [Nov. 16] 1959) reported good results with the use of sulfadiazine lipid emulsion, a long-acting form of the drug, in 29 children with acute infections, of whom 10 had acute upper respiratory infections, 7 had an acute upper respiratory infection with diarrhea, 6 had acute gastroenteritis, 3 had acute rysentery, 1 had bronchopneumonia, 1 had cystitis, and 1 had whooping cough. Sulfadiazine lipid emulsion was the only antimicrobial agent used, and it was given in a concentration of 10%. Children up to 2 years of age received 0.5 Gm. each morning in a single dose, and those above that age were given a single daily dose of 1 Gm. and an alkaline mixture. The duration of treatment varied from one to nine days. No patient with dehydration was included in this study.

Of the 29 patients 19 were cured, 7 obtained marked relief, and 2 obtained moderate relief. One patient had to stop taking the drug. Most of the patients responded well to treatment within two to four days. The drug was well tolerated and readily accepted. Side-reactions occurred in four patients. One child developed anuria, two developed oliguria, and one vomited the drug on the first day. The treatment was discontinued in the last patient. The anuria and oliguria disappeared when plenty of fluids and alkalies were given. The author recommended giving plenty of fluids orally and maintaining a chart of urinary output to guard against this complication.

Spleen in Thalassemia.—A. M. Mukherjee and coworkers (*J. Indian M. A.*, vol. 33, Dec. 1, 1959) examined 30 specimens of spleen from patients with thalassemia. Of these patients 21 were 10 years of age or less and 9 were between 11 and 25. The spleen was enlarged in all patients to about five times the normal size, and it was firm. The capsule was thickened in all, but evidence of perisplenitis was found in only four. The cut surface was red with prominent trabeculae. The splenic sinuses showed variable degrees of congestion on histological examination. The red pulp showed hyperplasia of cells of the reticuloendothelial system. Ten showed a moderate to large number of foam cells in large clumps; in 17 they were present in a smaller number; and 3 had no such cells. Extramedullary hemopoietic activity was also evident in the red pulp. This was marked in 6, moderate in 12, and slight in the rest.

The degree of hemopoietic activity was not related to either the degree of anemia, splenomegaly, or the proportion of fetal hemoglobin. The malpighian corpuscles were hyperactive in 4, normal in 9, and attenuated in 17. Splenomegaly in patients with thalassemia was thus essentially due to congestion of a greatly increased and dilated vascular bed, hyperplasia of reticuloendothelial cells, and extramedullary hemopoiesis. The presence of hemosiderin could be attributed to blood transfusions in most of the patients. The principal pathological changes consisted of congestion of the sinuses, reticuloendothelial hyperplasia, foci of hemopoiesis, atrophy of malpighian corpuscles, presence of hemosiderotic nodules, and increase of connective tissue.

Dihydroergotamine for Mumps.—Desphande and Vahalia used dihydroergotamine in the treatment of 25 patients with mumps and compared the results with those in another 25 patients who served as controls (*J. Indian M. A.*, vol. 33, Dec. 1, 1959). The duration of illness before admission varied from one to seven days. A single intramuscular injection of 1 cc. was given on the first day to adults and smaller doses were given to children. This was repeated after 48 to 72 hours in 10 patients in whom the swelling did not respond to the first injection. Most patients received treatment on the second day of illness. The drug did not seem to have a marked effect on the subsidence of fever, but the average period for the temperature to return to normal was 3.1 days in the control group and 2.5 days in the treated group. The average period for complete disappearance of the swelling in the two groups was 5.4 days and 4.0 days respectively.

Almost every patient showed a reduction in the size of the swelling within 24 hours of the administration of dihydroergotamine. In 33% of the patients receiving the drug, the swelling disappeared completely within 48 hours of treatment, whereas the swelling did not disappear in most of the patients in the control group until the third or fourth day after they fell ill. The associated orchitis in some patients was not affected by the drug, for in both groups it took about four days for this to subside. The pain in the parotid swelling subsided within 2.0 days in the control group and 2.3 days in the treated group, although other observers have noted prompt relief of pain after administration of this drug.

NORWAY

Comparisons of Angiographic Mediums.—Presthus and Bruland (*Acta psychiat. et neurol. scandinav.* 34:479-488, 1959) gave 35% iodopyracet compound to about half of a series of 133 patients for cerebral angiographies and 25% acetrizoate to the other half. The former compound contained 50% and the latter 68% iodine. The side-effects observed during the injection of contrast medium and within 24 hours after the examination were not remarkable in either group. No definite difference was noted in the image quality.

Ataractic Drugs.—J. B. Lien and co-workers (*Acta psychiat. et neurol. scandinav.* [supp. 136] 34:40-50, 1959) reported that, during the first three years in which ataractic drugs were used in the Norwegian Mental Hospital of Gaustad in Oslo, the turnover rose from 270 to 350 patients per year without increase in the ratio of first admissions to readmissions or increase in the number of beds. Of 1,600 patients treated in this period nearly 600 received ataractic drugs (438 were given chlorpromazine, and 120 were given reserpine). The authors believed that these drugs were the chief factor responsible for the improvement, as other factors remained fairly constant. In addition to chlorpromazine and reserpine, mepazine and 2-ethyl-crotonyl-urea were tried but on a smaller scale. In the analysis of the chlorpromazine-treated patients special consideration was given to the differing degree of response of the various diseases and symptoms. The significance of such differences was difficult to judge, but depressed, idle, and incontinent patients definitely responded less than did those in other categories.

Comparisons were made between chlorpromazine treatment and convulsive and insulin therapy, respectively, in the same patients. In many patients chlorpromazine seemed to be more effective than other drugs, but in some patients the opposite was the case. This investigation did not justify the complete replacement of the well-established methods of treatment by a method with chlorpromazine. A similar comparison made in 30 patients receiving reserpine showed the effect of the two drugs to be equal. A comparison of 405 of the chlorpromazine-treated patients and 120 reserpine-treated patients which were judged to be prognostically equal showed, however, that reserpine was less effective. Comparison of repeated chlorpromazine treatment showed inconstant results probably because of difference in intensity of treatment. The authors concluded that treatment with electric shock, insulin, and ataractic drugs all had their advantages and disadvantages, but none of them could be claimed generally to be superior to the others.

Prochlorperazine and Chlorpromazine.—Sundby and Lien (*Acta psychiat. et neurol. scandinav.* [supp. 136] 34:82-88, 1959) treated 118 chronically psychotic patients with prochlorperazine and compared the results with those of previous chlorpromazine treatment in 113 of them. About 67% had chronic mental disorders of more than five years' duration, and 75% were schizophrenic. Of the 89 women in the series, 11 had earlier insulin treatment and 74 had several series of electric convulsive therapy with an average of 46 treatments each. With prochlorperazine treatment 23 patients, or 19.5%, showed no improvement; 46 patients, or 38.9%, showed a slight improvement; 43 patients, or 36.4%, had marked improvement; and 6 patients, or 5.1%, recovered.

A better effect was observed with prochlorperazine than with chlorpromazine in 52 patients, or 46.0%. The same effect with both treatments was noted in 47 patients, or 41.7%. A better effect was obtained with chlorpromazine than with prochlorperazine in only 14 patients, or 12.4% of the 113 patients considered. The side-effects were more troublesome than those produced by chlorpromazine. The patients were more active and alert when given the maintenance dosage. There was no photosensitization, which in the present group had been one of the major complaints about previous chlorpromazine medication. Prochlorperazine appeared to be a useful tranquilizer with certain advantages over the older ones. The authors also found a combination of prochlorperazine and chlorpromazine to be of value in patients who were resistant to chlorpromazine and suffered from restlessness when taking prochlorperazine alone.

Iproniazid for Psychoses.—Lien and Fossum (*Acta psychiat. et neurol. scandinav.* [supp. 136] 34:91-97, 1959) treated 26 chronically depressed and 48 schizophrenic patients with iproniazid. Of the 74 patients, 24 were treated with chlorpromazine and 4 with reserpine before the investigation started. The maximum dose of 150 mg. of iproniazid a day was given for four months or more to 20 patients without causing unpleasant side-effects. Doses were reduced in most patients to 75 mg. a day, and in 21 the treatment was discontinued because the patient became worse or suffered from side-effects or because the desired result was obtained. In the chronically depressed patients about 70% improvement was noted, but in the schizophrenic patients the results were disappointing as there was improvement in only 10% and agitation in 30%. Such side-effects as lassitude, giddiness, and unsteadiness were noticed in 21 patients. The addition of reserpine increased the effectiveness of iproniazid in nearly half the patients receiving this combination.

SWEDEN

Ulcerative Colitis with Malignant Degeneration.—N. P. G. Edling and co-workers (*Acta radiol.* 52:123-128, 1959) reviewed the roentgenographic aspects of 26 patients who had ulcerative colitis with malignant degeneration. In 14 the entire colon showed signs of severe chronic inflammation when the diagnosis of carcinoma was made. In four, similar signs of ulcerative colitis in the entire colon were found at roentgenographic examinations three to six years before a carcinoma was discovered at operation or autopsy. Among the remaining eight patients five had involvement of the entire colon and one of the distal part of the colon at the first roentgenographic examination. On subsequent examinations the length of the colon was increased and the loops were again present, the appearances at times being normal. The roentgenographic findings indicated that a true improvement or healing of the inflammation had occurred, even as the malignant degeneration appeared. The histories of the two other patients suggested ulcerative colitis for several years, but the roentgenographic findings were normal except for the cancerous strictures. In 23 patients the inflammatory changes involved or had at some time involved the entire colon. The distal part of the colon was affected in one only. No final assessment was possible in the remaining two patients.

In this series 19 patients were between 17 and 31 and 7 patients between 40 and 58 years of age. The average duration of the disease until the discovery of malignant degeneration for all patients was 15.4 years. No constant roentgenographic findings were associated with ulcerative colitis and the subsequent development of carcinoma. Many patients had short, contracted colons, but in others the colitic changes had improved, or the colon had returned to normal length and haustration. The series also showed that severe changes in the wall of the colon due to colitis might heal without fibrosis of the muscular layer and the serosa. This healing, if it occurred, was, however, no guarantee against malignant degeneration, even though the patient's symptoms might have also decreased or even disappeared.

Gas Myelography.—Syringomyelia is a well-defined entity characterized by a dissociated reduction in sensibility with loss of appreciation of painful stimuli and temperature at an early stage, often in combination with atrophy of the hand muscles and segmental pain. Klefenberg and Saltzman (*Acta radiol.* 52:129-138, 1959) endeavored to ascertain by gas myelography whether enlargement of the spinal cord could be demonstrated in 28 patients with clinically typical syringomyelia. The results obtained were compared with those from gas myelograms of 20 normal subjects and 9 patients with intramedullary expansive processes without signs of syringomyelia. In most of the patients with syringomyelia on whom a technically satisfactory gas myelographic examination could be made, the revealed anatomy of the spinal cord differed from that of the normal controls. In patients with syringomyelia enlarged segments were noted in the cervical and upper part of the thoracic spine and atrophic areas were wholly or predominantly localized in the thoracic region. When both of these changes were present in the same patient the enlarged part of the cord was always situated cranially to the atrophic area. Syringomyelia with spinal cord enlargement but without atrophy could not be distinguished from an intramedullary expansive process of some other type.

The study of nine patients with intramedullary spinal cord processes without signs or symptoms of syringomyelia suggested that a combination of enlargement and atrophy might be a characteristic feature of syringomyelia as no change of this nature could be demonstrated in the spinal cords of the other patients. Tomography was a valuable aid when the caliber of large areas of the spinal cord was to be estimated by gas myelography. Theoretically a technique based on the use of high voltages should also offer great advantages. It was especially important in patients with syringomyelia in whom the cord lesions were distributed over large areas of the spine that the conditions for examination should permit a reliable estimation of all parts of the cord. The authors did not perform myelographic examinations with iodized oil in patients with clinically characteristic syringomyelia because they believed that gas myelography offered better opportunities for studying the spinal cord in patients with syringomyelia.

Toxoplasmic Encephalopathy.—According to Torsten Hafström (*Acta psychiat. et neurol. scandinav.* 34:311-321, 1959), toxoplasmosis may be either congenital or acquired. In the newborn infant it may be characterized by enlargement of the liver and spleen with or without jaundice, pneumonia, or myocarditis and in particular by encephalitis with intracerebral calcification, chorioretinitis, and hydrocephalus, the spinal fluid being xanthochromic and having an increased protein content. Retarded mental development and epileptic seizures often appeared as sequelae. In infants and young children epileptic seizures as well as impairment of vision and chorioretinitis may be symptomatic of congenital toxoplasmosis. The acute stage of acquired toxoplasmosis is occasionally associated with a severe course with high temperature and symptoms in various organs due to hematogenous spread.

Soon after the eruption interstitial pneumonia may develop with roentgenographically demonstrable, patchy changes in the lungs and interstitial myocarditis with infiltration and necrosis of individual muscle fibers. The lymphadenitis, which is usually localized in the cervical, axillary, and inguinal lymph nodes, may persist for several months. The most serious manifestation of toxoplasmosis is the meningoencephalomyelitis. In adults meningoencephalitis and a mild myocarditis may occur. Toxoplasma are found in the muscles, heart, brain, and spinal cord. Fibrillar twitching is occasionally observed. In the acute stage the protein content of the spinal fluid may be greatly increased. Usually there is no increase in cell count of the spinal fluid, which consists almost exclusively of mononuclear elements. The sugar content of the fluid varies, but it is generally below normal.

The author studied a series of 15 patients with toxoplasmosis, including 6 with acute encephalopathy. In each patient the onset was sudden and was characterized by marked malaise, lymphadenitis, and fever. The disease may have a prolonged course with remissions and exacerbations. The neurological symptoms may appear six to nine months after the onset of the disease.

Urinary Excretions in Mental Diseases.—Arne Bergsman (*Acta psychiat. et neurol. scandinav.* [supp. 133] 34:5-107, 1959) studied the 24-hour urinary output of epinephrine and levarterenol in 84 patients with mental disorders and a control series of 27 healthy subjects. The high epinephrine output during all manic periods and the low output in the endogenous depressions suggested that those two conditions were opposite not only with regard to the clinical manifestations but also biologically insofar as the excretion of catechol amines was concerned. It was assumed that an endogenous factor was present which caused both types of aberration, though it was possible that the emotions might be reflected in an altered catechol amine output and that the high excretion possibly gave rise to emotional disturbances. Since the chronic schizophrenics showed on the whole a normal output of epinephrine and levarterenol, there was no evidence of a relationship between chronic schizophrenia and the production and excretion of catechol hormones. The small urinary output of epinephrine and the high output of levarterenol in patients with senile dementia were assumed to be due to the disease as such and not to the patients' age. The high levarterenol level was thought to reflect the emotional state of these patients during the tests.

Chlorethiazol.—E. Osterman and co-workers (*Acta psychiat. et neurol. scandinav.* [supp. 136] 34:56-61, 1959) found that chlorethiazol (SCTZ), a drug chemically related to thiamine, the ethandisulphonate of 4-methyl-5-β-chlorethyl-thiazole, had anticonvulsant, sedative, and sleep-inducing properties. The functions of the autonomic nervous system and other biological constants were not affected by therapeutic doses. Clinically, it was most suitable in delirium produced by alcohol, manias, and diseases accompanied by pronounced psychomotor agitation and anxiety. The drug could also interrupt epileptic attacks. The authors used it to treat 16 patients until complete sedation was induced or for at least 10 days. No patients with mental aberration due to senility or arteriosclerosis were included. Four of the patients had varying degrees of mania. A physiological sleep rhythm was restored in practically all the 16 patients. These limited observations indicated that this substance could rapidly interrupt delirium tremens and prevent death. For this purpose SCTZ appeared to be superior to other forms of therapy. In addition it had a strong sedative effect on manic patients, although neuroleptic drugs or electroshock was also required.

UNITED KINGDOM

New Hypotensive Drug.—The recent introduction of the hypotensive drug, bretylium tosylate, has been followed by that of another, guanethidine, a report on which was made by Leishman and coworkers (*Lancet* 2:1044, 1959). A series of 25 patients of both sexes with hypertension of varying severity was treated with guanethidine for 3 to 11 weeks. Over half had previously received treatment with ganglion blocking drugs. All patients were initially hospitalized for about three weeks while the dose of guanethidine was stabilized. Owing to individual sensitivity and the prostrating hypotensive effect of an overdose, a test dose of 30 mg. was given initially and the dose increased by 10 or 20 mg. daily, according to the response. Dosage was reviewed weekly and if necessary increased or decreased by 10 mg. until the blood pressure was satisfactorily controlled. Six of the patients had hydrochlorothiazide in addition to guanethidine. The blood pressure of 13 of the 19 patients receiving guanethidine alone was satisfactorily controlled, and all but one of the 25 patients treated showed some reduction in blood pressure.

The results confirmed Dr. Irvine Page's observation that guanethidine given by mouth is a potent hypotensive agent, the effect being mainly postural, although some reduction in blood pressure occurs in the recumbent position. A fall in blood pressure was generally noted within four hours of taking the drug. Symptoms due to postural hypotension were common, but were immediately relieved by recumbency. The only noticeable side-effects were mild diarrhea, which developed within four hours of taking the drug and coincided with the first fall of blood pressure; myalgia and muscle weakness after giving large doses; and bradycardia. Guanethidine differs from bretylium tosylate in the greater duration of its hypotensive effect. The blood pressure of 18 of the 25 patients was satisfactorily controlled when they were last seen. The hypotensive effect of guanethidine is due to selective blockage of the sympathetic nervous system, probably by inhibiting the release or distribution of transmitter substances from sympathetic nerve terminals.

Health Service Reciprocity.—Full health service reciprocity is now given to nationals of the United Kingdom and its colonies by Norway, Sweden, and Yugoslavia. Since the inception of the National Health Service in 1948, the nationals of any country, whether resident in Britain or only on a visit, have been entitled to free medical care there. In Norway, full treatment, including medicines, is available in public hospitals to British subjects. A refund can be obtained of 75% of the amount of the physician's fees for treatment outside hospital, but there is a drug charge. The local health service office refunds the doctor's fee on production of a signed certificate and a British passport. In Yugoslavia, general medical, dental, and hospital services, as well as drugs prescribed, are free on production of evidence that the patient is British. Forms for intending visitors are issued by the Yugoslav consulate in London. In the Channel Islands, as in Britain, hospital medical treatment is free to visitors, and doctors' services are free, except in Jersey. An agreement for full health service reciprocity for British nationals in Denmark has been considered but not finally ratified. Limited health service facilities are available in France, Belgium, Holland, and Luxemburg for British subjects working in these countries if they are insured there.

Food and Indigestion.—P. H. Friedlander (*Brit. M. J.* Dec. 26, 1959) studied the diet of 70 patients with nonulcerous dyspepsia who attributed their dyspeptic symptoms to certain specific foods. Of these, 36 were given an "indigestible" food mixed with barium sulfate, and roentgenograms were made at intervals for three hours. Simultaneous studies of gastric acidity were also made in 21 patients. The studies were subsequently repeated, the patients being given a "digestible" food. An attempt was made to correlate the patients' symptoms during the tests with the findings from these investigations. Only four patients developed symptoms with the ingestion of the indigestible food. Gastroesophageal reflux was present in two, but no mechanism was apparent in the other two. One other patient had symptoms with both the indigestible and the control food, and three had symptoms with the control food alone. It was concluded that in these patients the composition of the food did not play an important part in the causation of their dyspeptic symptoms.

Phenol for Paraplegic Spasticity.—If a patient has the misfortune to be paralyzed in the legs, it is usually better for the limbs to be flaccid rather than spastic. Spastic paralysis is associated with painful spasms and often with incontinence. It can be converted into flaccid paralysis by division of the anterior spinal roots or by chemical anterior rhizotomy. After trial of various substances Nathan (*Lancet* 2:1099, 1959) decided that permanent destruction of all fibers of the anterior roots was best achieved by a 10 to 20% solution of phenol in glycerol or a 25% solution in iophendylate. The amount of solution injected was determined by the number of nerve roots it was designed to affect, 1 ml. usually affecting seven to eight roots, and 0.5 ml. two to three roots.

It might be thought that such strong solutions of phenol might be harmful, but no untoward reactions, such as meningitis or phenol poisoning, were encountered by Nathan, who treated patients with paraplegic spasticity due to multiple sclerosis, amyotrophic lateral sclerosis, compression of the cord by growths, collapse of the vertebrae, and congenital diplegia. He commented that the immense difference that removal of pain, spasticity, and spasms made to the lives of these severely incapacitated patients was striking. Their lives became bearable and enjoyable. With the lower limbs made flaccid they were able to go about in wheel chairs and enjoy social life.

The injection was made under radiologic control to determine with certainty into which space the phenol should be introduced. The patient was placed in the lateral position for lumbar puncture with the side to be treated lowermost, and, by means of a tilting table and use of hard cushions, the spine was positioned so that the roots to be treated were at the lowest point. The needle was inserted at the space corresponding to the exit foramen of the most important root, and the bevel was turned so that the injected fluid flowed on the nerve roots in their intervertebral foramina. The patient was left in the same position for half an hour to keep the solution in contact with the nerve roots. The postinjection treatment was the same as that used after a myelogram is made. An essential precaution was to keep the patient from lying flat to avoid any possibility of the solution reaching the head. Regeneration of nerve fibers after injection could occur, as spasticity returned in one patient after a year, necessitating a further injection.

Kelly and Gautier-Smith treated a series of spastic paraplegic patients by the same method with good results (*Lancet* 2:1102, 1959). They recommended, however, that the method be used only in bedridden patients.

Percutaneous Introduction of Cardiac Pacemaker.—Treatment of complete heart-block after open-heart surgery is to some extent eased by the use of an artificial pacemaker. Electrodes are placed at operation and removed only when a suitable ventricular rate has become established or when the conduction mechanism has recovered. Sometimes, however, the onset of heart-block is delayed until the postoperative period, and immediate restoration of an adequate ventricular rate by means of a pacemaker is essential. Reopening the wound and introducing an electrode into the myocardium may be dangerous.

Ross and Harkins (*Lancet* 2:1109, 1959) reported the case of a 14-year-old boy who had transposition of the great vessels and a common ventricle and who underwent exploratory ventriculotomy. By the second postoperative day a complete atrioventricular block had occurred that did not respond to drug treatment. Introduction of the cardiac electrode of an artificial pacemaker seemed unsafe, so an electrode was placed by percutaneous ventricular puncture. At the bedside, under sterile conditions, the indifferent electrode was implanted subcutaneously in the epigastrium and the myocardial wire electrode directed into the ventricular chamber through a hollow-bore needle inserted in the fifth intercostal space, 8.25 cm. from the midline. The needle was removed and, with the pacemaker turned on, the electrode was withdrawn until the heart rate matched the pacemaker impulse, indicating that the bare wire of the electrode was in contact with the myocardium. The current amplitude was then adjusted to be just above threshold level and the wire fixed to the skin by a suture. The electric pacemaker controlled the ventricular rate for 27 hours, at which time a satisfactory idioventricular rate had returned. The electrodes were removed after 57 hours. There was no clinical or radiologic evidence of bleeding from the puncture wound in the heart. The patient made a complete recovery with disappearance of complete heart-block on the 16th postoperative day.

Synthetic Penicillin.—The isolation and characterization of 6-amino-penicillanic acid has provided an approach for the synthesis of new penicillins. A new synthetic penicillin derived from this, the potassium salt of 6(α-phenoxy-propionamido) penicillanic acid, Broxil, was studied by Knudsen and Rolinson (*Lancet* 2:1105, 1959). They compared its absorption and excretion after oral administration with that of the potassium salt of penicillin V also given orally, and with the sodium salt of penicillin G given by intramuscular injection. The absorption of Broxil was superior to that of potassium penicillin V, judged by the serum levels and urinary excretion over a six-hour period. Serum concentrations of the former were at least twice those obtained with the latter after administration of equivalent doses. Doubling the dose of Broxil in the 125-mg. to 500-mg. range doubled the serum concentration. Blood levels obtained after its oral administration were at least equal to those obtained after the intramuscular injection of approximately equivalent weights of the sodium salt of crystalline penicillin G.

Migraine and Hypertension.—A survey of migraine in general practice was made by Dr. C. H. Walker of Liverpool (*Brit. M. J.* 2:1430, 1959). Among his 5,785 patients, 281, or nearly 5%, gave a history of attacks of migraine. Of these, 79% were women. Just over 50% had a family history of migraine. The criteria on which the diagnosis was made were unilateral recurrent headache, associated visual symptoms, nausea or vomiting, and a family history of migraine. Observing that 52% of a group of hypertensives also suffered from migraine, Walker investigated the incidence of hypertension in 150 subjects with migraine, comparing the blood pressure with that of 150 controls of the same age and sex distribution suffering from other conditions.

The difference between the mean systolic pressures and between the mean diastolic pressures, of the patients, age for age, with migraine and the controls was 10 mm. Hg. This difference is statistically significant. The incidence of migraine and hypertension in those over 40 years of age was then determined. It was found that the incidence of migraine rose as the blood pressure increased. A family history was also found to be common in both conditions, and the personality structure of the two disorders had several points in common. Patients with both conditions presented evidence of suppressed emotional conflict. Essentially the same mechanism is operative in producing the headache associated with hypertension and migraine—namely, dilatation and distension of the cranial arteries.

CORRESPONDENCE

PHOTODYNAMIC RESPONSE OF A NEW TETRACYCLINE

To the Editor:—On Sept. 28, 1959, a new tetracycline antibiotic, demethylchlortetracycline (Declomycin) was introduced to the medical profession. Much clinical and laboratory evaluation of this drug prior to its release established that, through its greater persistence in body fluids, reduced milligram administration achieves an equivalent or greater antibacterial activity, compared with other tetracyclines. Extensive pharmacological and laboratory toxicity studies failed to demonstrate any significant therapeutic difference from the other tetracyclines.

In the course of clinical evaluation the drug was distributed to 1,354 physicians. In the analysis of the 2,682 reports received to date, a photodynamic reaction to sunlight has been observed in 40 patients, most of whom were on prolonged therapy. In the analysis of these data every patient whose response might be even remotely related to this phenomenon was considered to represent a positive case. This reaction occurs to intense hot sunlight and is apparently similar to that seen with other tetracyclines, at least one of the phenothiazines, the sulfonamides, barbiturates, and gold salts. The sunburn reaction fades within a day or two on reduction of dosage or discontinuation of therapy. It occurs only on exposed parts of the body.

The average dosage of demethylchlortetracycline, in adults, is 600 mg. daily in divided doses, and it is thought to be unnecessary to exceed single doses of 300 mg. Because of the possibility of a photodynamic response to sunlight, patients should be cautioned, while on demethylchlortetracycline therapy, to avoid unnecessary exposure to intense sunlight. Should this reaction occur, demethylchlortetracycline administration should be discontinued until the sunburn clears, at which time therapy may be reinstituted, provided the patient exercises caution in exposure to the sun. Ambulant patients on maintenance therapy, the most likely to be exposed to sunlight, should probably receive a daily dose smaller than the recommended therapeutic dose. Because such a response is rare, it is necessary to expend great effort to verify these findings. Appropriate control studies are in progress under the supervision of competent investigators and the results of these investigations will be published as they become available.

Benjamin W. Carey, M.D.
Medical Director, Lederle Laboratories
Pearl River, N. Y.

TISSUE NECROSIS AND METARAMINOL BITARTRATE

To the Editor:—We have been disturbed by th implications and deductions in the article by Dipp and Dorney "Tissue Necrosis and Slough Produce by Metaraminol Bitartrate" in The Journal, Aug. 1959, page 1647. A patient was described as havin hemiplegia and thrombosis of the terminal aort with obstruction of the circulation below the lev of the renal arteries, which would be sufficient t have resulted in gangrene without invoking th treatment with metaraminol as a causative facto This patient received several intramuscular an subcutaneous injections without developing tissu necrosis. Nine hours after extravasation of a dilut metaraminol solution (30 mg. per liter), gangren developed in a previously pulseless extremity. Th agent implicated was the extravasated dilut metaraminol, like the straw that broke the camel back. Certainly, the straw cannot be blamed without implicating the other heavy loads carried b the camel.

We have been interested in tissue necrosis cause by levarterenol, from both an experimental and practical viewpoint (*J. A. M. A.* 165:444 [Oct. 1957; *Am. J. M. Sc.* 236:755 [Dec.] 1958). Zucke (*J. A. M. A.* 163:1477 [April 20] 1957) noted that intracutaneous injection of 1 ml. of levarterenol (1 mg per ml.) on the shaved abdomen of a rabbit regularly resulted in an area of ischemic necrosis. W (*Am. J. M. Sc.* 236:755 [Dec.] 1958) have also foun this to be invariably true; however, we could no produce ischemic necrosis with 1 ml. of metaramin (10 mg. per ml.) by this technique.

We have treated a large number of patients i coronary and surgical shock with intravenous injections of metaraminol (as much as 300 mg. i 1,000 cc. of fluid) in 10 times the concentratio used by Dippy and Dorney, or with intramuscula or subcutaneous injections of 1 to 2 cc. of metaraminol every hour, as needed, without one incident o ischemic necrosis. In certain instances we have use the intramuscular treatment as further depot support to the intravenous method. Although we hav not completely tabulated our cases, we can stat that while metaraminol is an effective sympathomimetic substance, its effectiveness does not approach that of levarterenol in patients with sever coronary shock. It is effective in postoperative shoc and in the hypotension that sometimes follow operation. We do not as yet have enough patient who had coronary shock treated with metaraminol by the intravenous route, supplemented by intrauscular injections when necessary, to make a state- ent of its efficacy. We have found no instances of chemic necrosis in a fairly large experience.

In the case described by Dippy and Dorney we lieve that the metaraminol extravasation had tle, if anything, to do with the subsequent de- lopment of gangrene. The stage was set for this fortunate development long before metaraminol as infused into the vein at the ankle. We believe at the use of an extremely useful therapeutic ent should not suffer because of questionable cumstantial evidence.

Louis Pelner, M.D.
Samuel Waldman, M.D.
1352 Carroll St.
Brooklyn 13, N. Y.

HYL ALCOHOL LEVELS IN THE BLOOD

the Editor:—In The Journal, June 27, 1959, ge 1108, Dr. Joseph Beeman disagreed with edemann and Bubowski (*J. A. M. A.* 170:47 ay 2] 1959), who stated that alcohol applied to skin has a negligible effect on the alcohol con- t of the blood drawn when alcohol is used as an iseptic. Dr. Beeman has found as much as 200 . of ethanol per 100 ml. of blood, or 0.20%.

paper of my own (*Am. J. Path.* 32:169 [Aug.] 9) on this subject indicates that alcohol on the has a very slight effect on the percentage of ohol found in the blood. It is more likely that Beeman's experience paralleled mine, namely, t the syringe had been rinsed with alcohol be- it was used to withdraw the blood. On two asions I found more than 1.0% alcohol in speci- ns, a percentage which would be incompatible h life, in persons who were very much alive.

ince writing this paper I have repeated my ex- iments, using needles of various sizes, and found t the most alcohol was found when the largest dles were used, namely, 21 gauge. Such needles uld not be used ordinarily; and even with this ge caliber I found only 0.008% alcohol in spite the fact that I did not simply daub the site with ohol but actually poured alcohol over the skin I immediately thrust the needle through a layer alcohol. I agree with Dr. Beeman that alcohol or er reducing agents should not be used when od alcohol tests are made, since this procedure uld cause needless arguments in court, but in zens of experiments I have not found that alco- applied to the skin had a significant influence the blood alcohol test result.

Herman A. Heise, M.D.
425 E. Wisconsin Ave.
Milwaukee 2.

DRUG NAMES

To the Editor:—The question of drug names is rapidly becoming a matter of international importance. As it stands now, there is international uniformity with respect to the systematic chemical name for new chemical compounds that may be introduced as drugs. These chemical names are thoroughly systematized and carry real structural meaning to chemists. On the other hand, to members of the health professions these chemical names are practically meaningless. Accordingly, relatively simple names for general public use have to be devised, and these are referred to as either "official," "generic," or "public." In addition, there are trade names, which are the legal property of the company exploiting the drug. Unfortunately, the public names for drugs vary in different countries. Sometimes this is due to trade name factors. Thus, the name adrenaline is a "public name" in Britain, but "Adrenalin" is a trade name in the United States. Accordingly, the public name for the drug in the United States is epinephrine.

It is time that an international effort be made to bring about some degree of unity in connection with public names for the same chemical compound which may be used as a drug in different parts of the world. The British Pharmacopeia Commission devises "Approved Names" for drugs, and "The intention is that if any of the drugs to which these Approved Names are applied should eventually be described in the British Pharmacopeia, the Approved Name should be its official title." Lists of these approved names are distributed monthly by the General Medical Council of Great Britain to all physicians, dentists, veterinarians, and pharmacists. These monthly lists of approved names are also distributed by the Royal Society of Medicine to its members. In this way, physicians in Great Britain have ready reference to the approved names of drugs and can have some idea of what it is, chemically, that they are giving their patients. These lists also contain proprietary names for cross reference.

The British Pharmacopeia Commission has set forth 10 guiding principles to be used in devising or selecting new approved names. It might be appropriate for American drug manufacturers, as well as for American organizations in the health professions, to consider these guiding principles regarding new approved names for drugs, so that some reasonable standards may be used for drug names in this country and some approach may be made to international uniformity in connection with drug names.

Chauncey D. Leake
American Association for the
Advancement of Science
Hamilton Hall
Ohio State University
Columbus 10, Ohio.

MEDICAL FILM REVIEWS

Carcinoma of the Stomach: Gastrectomy: 16 mm., color, sound, showing time 29 minutes. Prepared in 1958 by Waltman Walters, M.D., and William H. ReMine, M.D., Rochester, Minn. *Procurable on loan from Section of Photography,* Mayo Clinic, Rochester, Minn., or American College of Surgeons, 40 E. Erie St., Chicago 11.

The first few minutes of this film are devoted to a comparison of figures on resectability—three-year and five-year survival rates during a recent period (1940-1949) compared to survival rates in a series reviewed three decades previously. The techniques of radical subtotal gastrectomy and radical total gastrectomy are shown. The authors illustrate how the common duct is isolated and actually opened to prevent its injury during the radical resection of the stomach with a sizable cuff of duodenum. In both types of operations all of the nodes of the gastrohepatic omentum are removed along with the fatty tissue overlying the pancreas. Splenectomy is included in the radical subtotal gastrectomy and radical total gastrectomy. In the total gastrectomy, a loop of jejunum is brought posterior to the colon and anastomosed to the esophagus; jejunojejunostomy is then performed. The authors stress the danger of medical treatment of the chronic gastric ulcer, which they have found to be malignant in 20% of the patients. Early diagnosis for optimum results is properly emphasized. The film is well organized and the narration and photography are excellent. It is recommended for medical students, general practitioners, and surgeons.

Rescue Breathing: 16 mm., color or black and white, sound, showing time 21 minutes. *Produced in 1958 at the* Roswell Park Memorial Institute and the Buffalo General Hospital by and procurable on purchase from American Film Producers, 1600 Broadway, New York 19.

This film is designed to teach the techniques of rescue breathing (mouth to mouth and mouth to nose). An animated sequence shows how the tongue usually blocks the throat of an unconscious victim and how a rescuer can rectify this condition with rescue breathing. A series of dramatizations are shown which demonstrate how rescue breathing is used to save the lives of unconscious victims of drowning, choking, drugs, electric shock, gas asphyxiation, and chest injury. The film deserves much commendation for the way it overcomes the psychological obstacles that make it hard for many people to accept the idea of mouth-to-mouth breathing. The photography is good and the narration is intelligible. This film can be shown profitably to audiences at every level from fourth or fifth grade up. It will be of great interest to physicians who may not have had an occasion either to see the method demonstrated or to see the operation of an oximeter so well shown.

How To Do Rescue Breathing: 16 mm., black and white, sound, showing time 5 minutes. Consultants: Prof. Charles E. Silvia, Springfield College, and Dr. Harold T. Friermood, *National Council* Y. M. C. A.'s. *Demonstrated by* Ray T Smith, M.D. Produced in 1959 by and procurable on purchase ($49.50) from Seminar Films Inc., 480 Lexington Ave., New York 17.

The purpose of this film is to demonstrate and teach the performance of rescue breathing, including changing operators and moving the victim without use of special equipment. It begins by stressing the need for immediate action in cases o asphyxiation and then demonstrates the performance of the method explaining each step. It stresse the fact that rescue breathing can be done in an position which enables the operator to get at th victim's head and that it can and should be don even while the victim is being moved. This film good, short, and to the point. It demonstrates th procedure in a simple direct way. No indicatio advantages, or disadvantages are shown. The ph tography and narration are good. It will be prima ily of value to lay groups, provided some profe sional instruction accompanies the showing of t film.

NEW FILM ADDED TO A. M. A. MOTION PICTURE LIBRARY

Rehabilitation Adds Life to Years: 16 mm., color, sou showing time 30 minutes. Presented by the American Me cal Association, Committee on Rehabilitation. Produced 1959 by Reid H. Ray Film Industries, Minneapolis. P curable on loan (no service charge) from Motion Pict Library, American Medical Association, 535 N. Dearb St., Chicago 10.

This film is designed to show the medical prac tioner the important role of rehabilitation in t total patient care, organization of rehabilitati services in the community, and the application services to individual patients and to demonstra the type of disability requiring referral to a mo elaborate rehabilitation center. The key position the family physician in rehabilitation is stresse It shows the rehabilitation in the community h pital of a hemiplegic housewife and of a pati with a myocardial infarction, and then the progr of a paraplegic patient in a rehabilitation center depicted. The philosophy, organization, and te niques of rehabilitation in the local community a well presented. The multifaceted approach of t rehabilitation center is well shown. The film is excellent presentation of the need for rehabilitati and the various resources for accomplishing t goals. The color photography is very good. The fi is recommended to be shown to physicians.

ILLUSTRATED FILM REVIEWS

REHABILITATION ADDS LIFE TO YEARS

This film was sponsored by the American Medical Association and was produced under the auspices of he Committee on Rehabilitation. Its purpose is (1) to acquaint the practitioner with the magnitude of the ehabilitation problem from the standpoint of patients' needs and the opportunities that physicians have to ncrease their services by helping in the rehabilitation of their patients; (2) to show the medical profession he techniques necessary to organize medical and other phases of rehabilitation at the community level; 3) to show a practical example of how the practitioner can see to it that his patients receive these rehabiliation services which have been organized in the community; and (4) to indicate the type of rehabilitation roblems which warrant referral of the patient to a comprehensive center.

The film shows how the rehabilitation center can serve the patient while still respecting the referring phyician's interest in his patient. It is designed primarily for a medical or other related professional audience.

Fig. 1.—This doctor's career seemed to have been ended poliomyelitis when he was 30 years of age, but with etermination and rehabilitation he is now able to practice a pathologist.

Fig. 2.—This victim of coronary thrombosis was treated in his own small community by the family doctor and was put back to work by his employer in a job he could do.

Fig. 3.—Hydrotherapy is used as part of the treatment of is rheumatoid arthritis patient. Hip arthroplasty, theraeutic exercises, and occupational therapy rehabilitated her useful homemaking for her family.

Fig. 4.—The medium-sized community hospital provides occupational therapy which helped this patient, who had a stroke, master her disability.

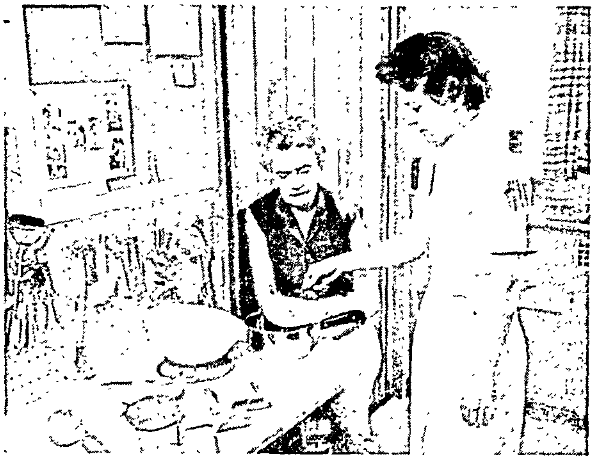

Fig. 5.—In the case of the hemiplegic, kitchen chores with one untrained hand are skills that must be learned. *Assistive devices are used.*

Fig. 6.—This victim of an automobile accident was sen from his smaller community to a comprehensive rehabilitation center.

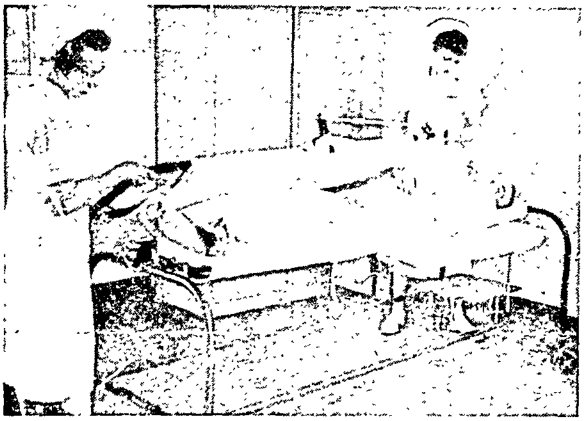

Fig. 7.—At the rehabilitation center, the patient soon left *his frame to begin therapeutic exercises to strengthen the* upper extremities and to begin gait training.

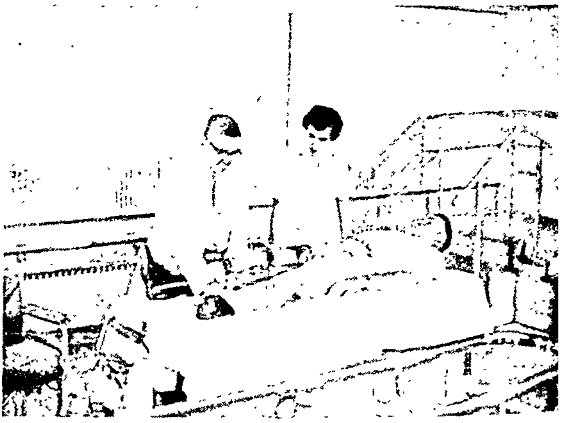

Fig. 8.—After fitting with braces, ambulation was accomplished. The patient then received *prevocational* training and subsequent full-time employment.

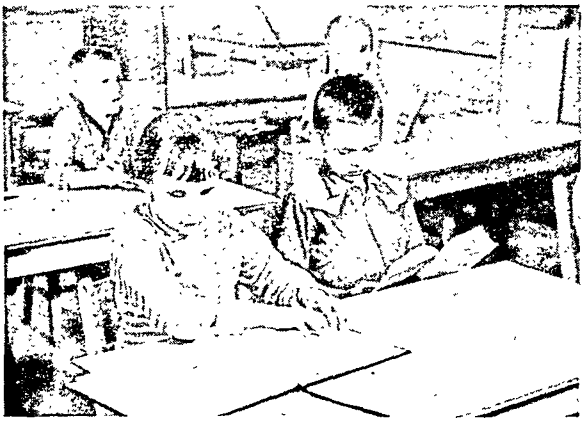

Fig. 9.—*Community services should be utilized. Here, the* department of special education in the local school is used in the training of the blind and those with partial sight.

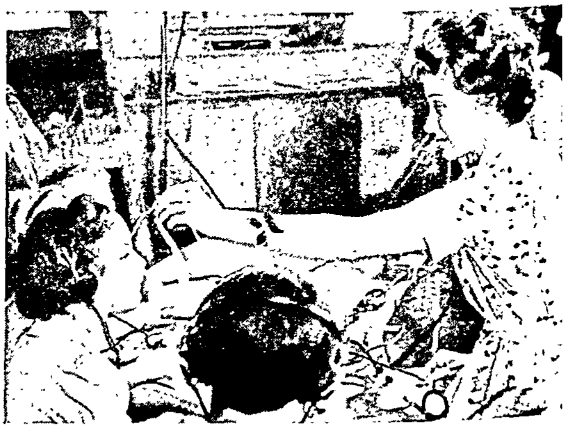

Fig. 10.—*Speech training in a class for* hard-of-hearing and deaf children is part of the community school system's special education program. Rehabilitation calls for the combined efforts of many disciplines so that real meaningful *life may be added to every patient's years.*

MEDICAL LITERATURE ABSTRACTS

SURGERY

A Study of Pancreatography. M. Birnstingl. Brit. J. Surg. 47:128-139 (Sept.) 1959 [Bristol].

The studies were undertaken to correlate the roentgenologic appearances of the duct system of the pancreas with the histological findings in patients without overt pancreatic disease. The intention was to provide a basis for the interpretation of operative pancreatograms, obtained in the living subject, and to investigate the incidence of epithelial metaplasia and hyperplasia in routine autopsy material. The material was obtained at autopsies at St. Bartholomew's Hospital, London, from adult subjects dying of a variety of diseases. Apart from the exclusion of cases of known primary pancreatic disease, an attempt was made to examine organs from consecutive patients. The series consisted of 94 male and 56 female subjects. The pancreas, together with the duodenal loop, was removed from the body, and a probe was passed down into the duodenum, through the common bile duct, to locate the papilla. The latter was then lifted away with toothed dissecting forceps, and the duodenal mucosa was dissected back as a cuff until about 1 cm. of the wall of the ampulla was exposed. By making a nick in the inferior aspect of the ampulla, the main pancreatic duct could be entered. A 2-mm. cannula was tied into the duct, and radio-opaque medium was injected. An average volume of 2 ml. was required to fill the ducts. In a few specimens injection by the above route was unsuccessful, but was achieved either by cannulation of a prominent lesser duodenal papilla or by retrograde injection along the main duct after transection of the tip of the tail of the pancreas.

After roentgenography the organs were placed for 24 hours in a formaldehyde solution for fixation. The material was sliced at about 0.5-cm. intervals and examined for gross abnormality, after which an average of 4 histological sections were made from each pancreas. The anatomic variations which influence the interpretation of pancreatograms were reviewed on the basis of combined roentgenologic and histological studies. The main pancreatic duct showed variations in caliber, ranging between maximum diameters of 1.8 and 9.2 mm.; the upper limit of the normal diameter of this duct is about that of an ordinary lead pencil (8 mm.). Appearances of isthmic stenosis, terminal dilatation, and an undulating outline in this duct were occasionally seen and represent anatomic variants. The accessory pancreatic duct communicated with the main ductal system in 68% of specimens, but only appeared patent in 55%. Dilatation and irregularity of the secondary pancreatic ducts were commonly seen on the pancreatograms and produced an appearance of pancreatectasis in a few specimens. These variations closely reflected the development of hyperplastic and metaplastic changes in the ductal epithelium.

Columnar epithelial hyperplasia was seen in 29% of organs; the change was most frequent in the secondary ducts and in the ampullary region of the accessory pancreatic duct. It was most common in the form of intraductal proliferation, but hyperplasia of mucus-secreting glandular structures related to the ducts was also seen. *These variants* resemble cholecystitis glandularis proliferans, with which they are comparable. Subclinical focal pancreatic necrosis was encountered in 5 specimens, in which it was apparently related to the presence of hyperplastic epithelial lesions in the ducts. Squamous epithelial metaplasia was present in 10% of organs, although never to the extent shown by columnar hyperplasia, with which the change was generally associated. In view of the wide range of roentgenologic and histological appearances in an apparently normal autopsy material, the author feels that pancreatograms obtained during abdominal surgery require cautious interpretation.

Adenocarcinoma of the Large Bowel: 1,340 Cases with 100 Per Cent Follow-Up. V. A. Gilbertsen. Surgery 46:1027-1042 (Dec.) 1959 [St. Louis].

The author reports on 1,340 patients with adenocarcinoma of the large intestine, who were seen at the University of Minnesota Hospitals in Minneapolis between 1940 and 1955. Of the 1,340 patients, 693 had primary lesions in the rectum, 605 had primary lesions in the colon, and 42 had lesions in several different anatomic sites of the large intestine. The operative rate was 98%. The over-all resection rate was 84%, with 87% for adenocarcinoma of the colon and 82.3% for adenocarcinoma

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The place of publication of the periodical appears in brackets preceding each abstract.

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of the rectum. The general composition of the group indicated that patients were somewhat older than in the usually reported series. Operative, resection, and survival rates, however, compared favorably. Two-thirds of the patients with carcinoma of the colon died of their disease without 5-year survival; 32% of the patients survived cancer-free 5 years. When patients underwent excisions for cure, however, about two-thirds of those with cancers of the colon and one-half of those with cancers of the rectum survived 5 years. When patients with Dukes A lesions are considered, 83% of those with colon lesions survived 5 years, including 100% with lesions of the splenic flexure, hepatic flexure, and transverse colon.

The most favorable prognosis after excision for cure was associated with lesions of the transverse colon (90% 5-year postoperative survival); the least favorable prognosis was associated with lesions of the rectum (49%). The popular reluctance against employment of larger operations for large cancers receives little support; enlarged excisions allowed substantial survival of patients whose disease might otherwise have been inoperable for cure. Curative excisions in patients, aged 44 years or less, were followed by acceptable survival rates. This was not noted in patients, aged 80 years or older, except those few with lesions of the transverse colon. Palliative excisions were associated with measurable palliation, as were colostomies performed without resection; cecostomy, catheter enterostomy, and ileostomy, however, were not.

The Development of Carcinoma of the Large Intestine in Ulcerative Colitis. I. M. P. Dawson and J. Pryse-Davies. Brit. J. Surg. 47:113-128 (Sept.) 1959 [Bristol].

This survey is based on a study of 663 patients with ulcerative colitis, who attended the Gordon Hospital, London, in the 11¾ years up to December, 1958. The records of 735 patients with suspected colitis were examined, and in 663 cases the diagnosis was considered proved. The final diagnosis of ulcerative colitis was based on proctoscopy, sigmoidoscopy, and the roentgenologic appearances after barium enema. In 284 cases there was confirmation of ulcerative colitis by rectal or colonic biopsy, and in 183 a part or all of the colon was examined after resection.

Carcinoma of the large intestine was found in 19 of the 663 patients (2.9%) with ulcerative colitis. There were 409 (61.7%) women and 254 (38.3%) men; and in the carcinoma group there were 12 women and 7 men. The average age of the patients at the time of onset of the symptoms of colitis was 35 years, but more than 12% were less than 21 years old. In the carcinoma patients the colitic symptoms appeared at an average age of 26.1 years; 7 patients were less than 21 years old. The average duration of colitic symptoms was 9.6 years, but in the carcinoma group the average duration was 17.8 years, and in 13 of the 19 carcinoma patients symptoms of colitis had existed for more than 15 years prior to the discovery of carcinoma. The development of carcinoma appears to be related to the duration of colitis rather than to the age at onset. The average age at diagnosis of cancer was younger than the usual age for cancer of the large intestine.

While there was no specific picture indicating the presence of carcinoma in ulcerative colitis, the existence of a stricture did seem to be an important feature. In 7 cases strictures were diagnosed prior to operation; in 3 of these the strictures had developed more than a year before the carcinoma was diagnosed, and in 2 others the strictures probably preceded the growth. Although some investigators are of the opinion that strictures generally result from the carcinoma, the present authors believe that carcinomas sometimes arise at a preformed stricture and that the presence of a stricture requires a careful survey for carcinoma.

In 10 patients the carcinoma was in the rectum, and in 7 in the colon; in 2 cases the primary site was not determined. The growth was well differentiated in 4 cases, moderately differentiated in 6, and poorly differentiated (or anaplastic) in 7. Early spread beyond the intestine and early metastasis were common features. Carcinoma in the colon developed on a basis of chronic active ulcerative colitis, while carcinoma of the rectum developed in active or quiescent colitis. Microscopic features of the carcinoma are discussed, and the possible origin from "buried" epithelium considered. Polyps were frequently associated with the carcinoma. They were of adenomatous, pseudopolypoid, and transitional forms. The possibility of transition from pseudopolyp to true adenoma and carcinoma is discussed. The prognosis of carcinoma in ulcerative colitis is poor. Cases of ulcerative colitis, both chronic active and quiescent, of long duration, require careful, regular follow-up, with biopsy, if possible, especially in the presence of stricture.

Intestinal Lipomatosis. C. S. Ling. C. Leagus and L. H. Stahlgren. Surgery 46:1054-1059 (Dec.) 1959 [St. Louis].

The authors report on a 60-year-old woman with diffuse symptomatic submucous lipomas of the intestine. She was admitted to the Philadelphia General Hospital because of copious bright red rectal bleeding. A barium enema revealed a polypoid lesion of the terminal ileum with ileocecal intussusception, but the patient refused laparotomy and was discharged. Six years later she returned to the hospital and complained of intermittent lower abdominal pains of about 8 months' duration. The pains were cramping in nature and were relieved by the passage of flatus or feces, but generally subsided spontaneously. She also had nausea and vomiting in recent weeks and had noted increasing constipation. A firm, movable, slightly tender fusiform mass was palpable in the right lower quadrant in the area of the cecum. Peristalsis was normal. Numerous polypoid lesions were identified throughout the colon and the small intestine by barium enema examination. Surgical exploration revealed numerous intraluminal, polypoid, soft, movable tumors of the small intestine and colon. Two areas of ileoileal intussusception were noted, and both were easily reduced. In each, a large polypoid intraluminal mass was palpated at the intussuscepting point. A resection of the ileocecal intussusception and the distal ileum which contained the most concentrated area of polyps was performed. Enterotomies were then performed at the side of the 2 ileal intussusceptions. Lipomas measuring about 2 by 3 cm. were shelled out from the submucosa. Postoperatively the patient did well and was discharged on the 10th postoperative day. Pathological examination of the operative specimen, consisting of 195 cm. of the terminal ileum and ascending colon, revealed 107 submucosal sessile and polypoid lipomas of sizes varying from 5 mm. to 5 cm. in diameter. They were scattered throughout the intestine, some singly and others in clumps. Microscopic examination showed lobulated collections of mature fatty tissue, mostly submucosal in location.

Symptomatic lipomas usually arise in the submucosa and project into the lumen. Symptoms are usually due to intussusception caused by lipoma. Bleeding due to ulceration or trauma to the mucosa overlying a lipoma is less common. Lipomas of the colon which produce symptoms occur twice as frequently as lipomas of the small intestine. Operative treatment should be conservative and should consist of enterotomy and shelling out of the lipomas or limited resection of the intestine in which the greatest concentration of lipomas exists. The prognosis is good, but symptoms of intestinal obstruction or bleeding may recur. A familial incidence has not been established.

Diverticulosis of the Duodenum. J. D. Bloom and W. J. Gillesby. Am. Surgeon 25:931-936 (Dec.) 1959 [Baltimore].

The authors report on 120 patients in whom a diagnosis of diverticulosis of the duodenum was made at Hines (Ill.) Veterans Administration Hospital between 1950 and 1954. These patients were subdivided into 5 groups. The first group, consisting of 56 patients, had symptoms probably due to other abnormal gastrointestinal conditions. The second group consisted of 9 patients with symptoms which could have been due to other abnormal gastrointestinal conditions, but less definitely so, since these included such ailments as hiatus hernia, gastritis, prolapsed gastric mucosa, or cirrhosis; they often produced a vague symptom complex and rendered the actual source of the symptoms less certain, particularly since none of these 9 patients underwent surgical treatment. The third group consisted of 20 patients in whom the diagnosis was established by x-ray, but who, at the time of discharge, carried no other diagnosis to explain the symptoms presumably present to warrant a barium meal. The fourth group consisted of 30 patients who were admitted with varying abdominal complaints which led to such diagnoses as gallbladder disease, peptic ulcer, or hiatus hernia; these diagnoses were not established during the course of the examination, but barium studies revealed duodenal diverticula. In general, the patients of group 4 responded well to a mild ulcer regimen and were discharged; a few who responded poorly were labeled psychoneurotic; in most patients of this group, duodenal diverticula were not considered a cause of their symptoms. The fifth group consisted of 5 patients who underwent surgical treatment for symptoms believed to have arisen from diverticula; of these, 2 had simple excision, and 3 had gastric resection. Bleeding was difficult to control during dissection, and one patient, who had excision of a diverticulum, died of a sudden hemorrhage on the 9th postoperative day.

Particular attention to the last 3 groups led to the assumption that the symptoms of the 20 patients in group 3 were caused by diverticula. There was almost constant complaint of epigastric pain which occasionally radiated to the right upper quadrant and to the back. This pain frequently occurred before meals, but in several patients it occurred about half an hour after eating. Vomiting occurred in about 33% of the patients. More than half of them lost 10 to 20 lb. (4.5 to 9.1 kg.) in weight. In general, the symptoms were so mild and vague that in none of the patients was the diagnosis made before x-ray examination. In 60% of the patients the diverticula were located in the second portion of the duodenum; in 35%, in the third portion; and in 5%, in the fourth portion. They were solitary in 75% of the patients, and multiple in 25%. Two of them were subsequently shown to arise from the stomach near the pylorus. The retention of barium, as shown on the 5-hour roentgenogram, in 54% of the patients in the last 3 groups is considered evidence that the diverticulum is the producer of the symptoms. The pathogenesis is probably stasis of food particles in the lumen with supervening bacterial overgrowth and resultant inflammation. The incidence of duodenal diverticula is probably greater than is indicated by these figures. When there is a well-adjusted patient, giving a history of pain, vomiting, and loss of weight intermittently over a period of a year, and when roentgenograms show a diverticulum with a fair amount of retention after 5 hours, it is reasonable to think that a causal relationship exists. If bland diet and administration of antacids cannot keep symptoms to a minimum, surgical excision should be considered.

Nature and Treatment of Stenosing Tenosynovitis. M. Zwicker. Deutsche med. Wchnschr. 84:2161-2164 (Nov. 27) 1959 (In German) [Stuttgart, Germany].

Before describing his own observations on 54 patients with stenosing tenosynovitis, the author mentions de Quervain's description of the condition in 1895, and reviews the topographic anatomy of the wrist joint. All but 6 of his 54 patients were women: 21 were housewives; 5, nurses; 5, office workers; and the rest, dressmakers, domestics, and the like. Stenosing tenosynovitis is the result of fibrous or cartilaginous narrowing of the common tendon sheath of the abductor pollicis longus and the extensor pollicis brevis muscles. The process interferes with the free play of the tendons and produces annoying pain in the thumb, the hand, and the forearm. The patients are mostly women of middle age or older, whose work involves certain repetitious manipulations. Since conservative treatment is rarely successful, the author recommends early surgical treatment. The operation can be carried out under local infiltration anesthesia. The indurated portions of the tendon sheath are incised or excised. The results of this treatment proved excellent in the patients presented.

Leiomyosarcoma of the Duodenum: Case Report and Summary of Literature. R. R. Bradham. Am. Surgeon 25:950-957 (Dec.) 1959 [Baltimore].

The author reports on a 47-year-old man with leiomyosarcoma of the duodenum, who was admitted to the Medical College Hospital in Charleston, S. C., with the chief complaint of rectal bleeding. Associated with the bleeding were symptoms of dyspnea, marked fatigability, weakness, malaise, and several attacks of syncope. There was no history of weight loss. Upper gastrointestinal roentgenograms showed in the third portion of the duodenum, a segment, measuring roughly 7 cm. in length, which was narrowed as though by an intramural tumor. There was no delay in the passage of barium, and the pattern of the small intestine was otherwise normal in appearance. Laparotomy was performed, and a tumor, measuring 6.5 by 4.5 cm. and arising from the inferior wall of the third portion of the duodenum, was easily mobilized and resected with adequate margin. No metastases were found. Primary end-to-end anastomosis was done. Microscopic examination of the operative specimen revealed, within the submucosa and fibromuscular wall, a poorly defined neoplastic mass, composed of closely packed bundles of spindle and fusiform cells of smooth muscle origin, in which there were nuclear atypicalities and increased mitotic activity consistent with the diagnosis of leiomyosarcoma o the duodenum. The patient made an uneventfu recovery, and there has been no recurrence up t the time of publication of this report.

Fifty-three additional cases of leiomyosarcom of the duodenum were collected from the literature. The age of the youngest patient was 25 year and that of the oldest was 80 years. There was a equal distribution in the 2 sexes. Duration of symptoms varied from a few days to 13 years. Weaknes and ease of fatigability were the most commo symptoms. Fifty per cent of the patients ha marked gastrointestinal hemorrhage, as manifeste by melena and hematemesis.

Roentgenograms are extremely helpful in makin the diagnosis of leiomyosarcoma of the duodenum If the tumor is predominantly intraluminal, a fil ing defect with rounded borders and distortion overlying mucosa may be found. Extralumin tumors show pressure defects and interruption peristalsis. Ulceration can occur with either typ and, as the tumor enlarges, fistula and sinus tra formation are common. Choice of treatment is e cision of the tumor with adequate margins of th duodenum and any invaded organs.

A Clinical Study of 25 Patients with Carcinoi Tumors of the Rectum. G. W. Peskin and M. Orloff. Surg. Gynec. & Obst. 109:673-682 (Dec 1959 [Chicago].

The clinical and pathological characteristics carcinoid tumor of the rectum in 25 patient treated at the Hospital of the University of Pennsy vania in Philadelphia between 1933 and 1958, a reported. There were 15 men and 10 women, wi ages ranging from 20 to 79 years. The greatest fr quency (13) was in the 40-to-59 age group. Ev dence of malignancy was found in 10 patients i whom the tumor extended into or beyond th muscle coat of the intestine, as demonstrated b the biopsy specimen obtained at sigmoidoscop Six patients showed metastases at laparotomy, an in one other metastases developed after the oper tion. In 15 patients the diameter of the tumor wa less than 2 cm.; in the other 10 it was 2 cm. or mor Nine of the 10 tumors measuring 2 cm. or mor were metastasized and/or extended locally. Of th 15 tumors measuring less than 2-cm. diameter, onl one showed signs of malignancy and extende through the intestinal wall, without spreading t lymph nodes or other organs. The most frequen symptoms among the 25 patients reported wer pain, bleeding, and constipation, each occurring i about one-fourth of the patients. One-third of th patients had no symptoms; their rectal tumors ha been discovered incidentally during a routine examination for some unrelated abnormality.

Three forms of treatment were used, namely local excision, radical resection, and palliativ measures, such as colostomy. Fourteen patient whose tumors had less than a 2-cm. diameter were treated by local excision. All of them were in good health, with no signs of recurrence at the time this article was written (the postoperative period varied between 1 month and 14 years). The 15th patient with a tumor of less than 2-cm. diameter underwent abdominoperineal resection, mainly because of an associated rectal polyp showing carcinomatous changes; the patient was well 5 years after the operation. Four patients with extension of the tumor into the muscle layer of the intestine also underwent abdominoperineal resection. Three of them were alive and well at the time of this survey (3½ years, 2½ years, and 2 months, respectively, after the operation). One patient died of widespread metastases 7 months after the operation. Six patients with large lesions received only palliative treatment. All of them died of cancer, 5 within 2 years from the initial treatment. The 6th patient lived 9 years before he succumbed to widespread metastases. The authors conclude that 2 factors should influence the surgeon in the direction of radical therapy. These are evidence of extension of he carcinoid into or beyond the muscle coat of the ntestine and a tumor measuring 2 cm. or more in diameter.

Compression Arthrodesis of the Ankle. A. H. Ratiff. J. Bone & Joint Surg.41-B:524-534 (Aug.) 1959 London].

The author presents an analysis of the results of compression arthrodesis of the ankle, which requires a transverse incision with division of the extensor tendons. Fifty-nine operations, of which 4 were bilateral, were performed on 55 patients reated at the Royal Infirmary in Manchester, Engand. The majority of the patients were between 18 and 60 years of age. The patients were followed up for from 1 to 9 years after the operation. Arthrodesis was performed on 21 patients with osteoarthritis, 12 with tuberculosis, 7 with poliomyelitis, 7 with spastic hemiplegia, 3 with cluboot, and 3 with chronic arthritis; 6 miscellaneous conditions were the cause for the operation. Twenty-nine of the 59 ankles were immobilized for only weeks, and the remaining 30 ankles required immobilization for from 9 weeks to 9 months. As a result of this study, it is now recommended that he compression pins be removed 4 weeks after the operation and that a below-knee walking plaster cast be applied. All fixations should be discarded 8 weeks after the operation, regardless of the radiographic appearances.

Bony fusion occurred in 54 of the 59 ankles. In particular, it occurred in all the patients with osteoarthritis. In 4 patients the operation resulted n fibrous ankylosis, but the patients were satisfied with the result, and it was impossible to distinguish these ankles from those in which bony fusion had occurred. In one patient the fusion failed; arthrodesis had been performed for a Charcot's joint; the joint surface came apart after removal of the pins 4 weeks after the operation, but bony union was secured after a further operation. Thirty-four patients had no pain after the operation, 16 noticed a slight ache after intensive exercise, and 2 complained of pain. The gait was studied in 30 patients and was classified as perfect in 24; 4 patients showed a mild limp, and 2 (both over 60 years of age) showed a marked limp. In this series there was no serious complication, and no death occurred from the operation.

Investigation for any consequent ill-effects of the transverse incision showed that loss of sensation was usually present, but in no patient was it a serious complaint. No evidence of impaired circulation was found in any patient. The action of the extensor tendon of the toes and tibialis anterior, which was studied in 26 feet, was good in 23. In the remaining 3 feet the tendons were weak, and the results were regarded as poor. A lateral radiogram of the foot and ankle was taken of every patient, standing barefoot with the knees extended. The plane of the sole was outlined by a metal wire. The angle between the plane of the sole of the foot and the line of the tibia was measured, and this was defined as the position of arthrodesis. The ankles of all patients (except one) with a perfect gait were arthrodesed, either exactly at the right angle or in slight calcaneus or equinus position.

NEUROLOGY & PSYCHIATRY

Psychological Implications of Hysterectomy. S. H. Sturgis and H. S. Robey. Connecticut Med. 23:786-792 (Dec.) 1959 [New Haven].

When a condition is found in the gynecologic clinic that demands hysterectomy, the resident surgeon explains the diagnosis and the operative procedure. A few patients accept the news with apparent relief. More often, however, the connotations of "operation" and "hysterectomy" induce an emotional black-out in which all further explanations and reassurances are rejected. There is little time in a busy clinic to allow for adequate recovery from this state, and misunderstandings often remain uncorrected. During an investigation of the influence of emotional factors on recovery from hysterectomy, one of the authors interviewed a selected group of 20 patients who had been advised to undergo hysterectomy. In the belief that an operation on the reproductive organs strikes deeply at a woman's psychological integrity, these women were seen before admission with the purpose of giving them a chance to talk freely about their proposed hospital experience. A quiet noncommittal "opening of the door" to whatever each woman wished to express first became the most favorable approach. Feeling genuine sympathy for what the patients were going through, and using psychiatric social-work techniques, the social worker established a warm and friendly relationship.

Each of the 20 patients, unprepared for what she would find in a social-work interview or in herself, was given the chance to voice her concerns and fears. The drive to express these and the accompanying anxiety varied according to each woman's emotional involvement and the strength of her personality defenses. These 20 clinic patients varied widely in education, social background, race, and religion. They showed also a considerable variation in duration and severity of symptoms and extent of pathology. The interviewer purposely did not review the medical history and physical findings. She was assured by the referring physician only that the tentative diagnosis was that of benign uterine disease. Just as every woman differed, so the process of each interview differed. The range of response ran from a denial, or blocking even, of knowledge of the planned operation to a "sensible" acceptance of the news; from confused thinking to obvious mastery of the situation; from blind fears and superstitions to controlled reality questioning and evaluation.

The interview itself apparently gave all the women a sense of support and relief, and the authors felt that the readiness of some to accept psychiatric aid stemmed from satisfactions arising out of the interview. Although these were clinic patients, the authors believe that similar reactions, with different coloring, are probably aroused to a certain extent in private patients faced with the same news. Since these women seemed to profit from the opportunity to verbalize their feelings about the anticipated operation, the authors suggest that a general hospital might consider making available some similar preoperative interview opportunity for patients anticipating major surgery.

The Epileptic in Relation to Pregnancy. H. Dimsdale. Brit. M. J. 2:1147-1150 (Nov. 28) 1959 [London].

The author reports on 5 women in whom epileptic attacks occurred in relation to pregnancy. As a result of better therapeutic and social management, the epileptic woman has increased opportunities of marriage, and epilepsy is likely to become a more frequent complication of pregnancy. The effect of pregnancy on the epileptic patient is unpredictable. The attacks may increase in number or remain unchanged. Reduction in incidence of convulsions is often related to better therapy. Epilepsy associated with menstruation usually persists in pregnancy. When attacks first appear in pregnancy (gestational epilepsy), these are likely to be partial or focal in character. The metabolic changes in pregnancy, such as hydration, hyperventilation, and dilution of calcium, sodium, and magnesium in the serum, favor an increase of convulsions. The variations in excretion of aldosterone are probably compensatory to fluctuation in sodium intake. Excessive gain in weight and sodium retention may precede the onset of increased convulsions. A genetic or constitutional factor is important in the appearance of seizures in toxemia of pregnancy. A persistent epileptic tendency may result. Status epilepticus is a rare but grave complication, especially when occurring in later pregnancy, and has a higher mortality than eclampsia. The onset of status epilepticus in pregnancy may be the first manifestation of a cerebral dysrhythmia.

The epileptic woman should not be discouraged from pregnancy, unless her attacks are difficult to control in the nonpregnant state, but there is no excuse for regarding this complication of pregnancy lightly. Antenatal care should be as thorough as in suspected toxemia of pregnancy. Management of pregnancy consists of suitable anticonvulsants, with dosage corrected for gain in weight. Phenobarbital in a slowly absorbed capsule form (Spansule), given at night, may carry the patient over the morning hours when retention of tablets is difficult, owing to vomiting. Anemia should be treated, and macrocytic forms, whether due to pregnancy or administration of anticonvulsants, will require administration of folic acid. Excessive gain in weight should be controlled by diet, restricted salt intake, and rest. If the response is unsatisfactory, the use of acetazolamide or ion-exchange resins should be considered. Status epilepticus may require the use of continuous intravenous administration of anticonvulsants, with controlled respiration. Investigation of gestational epilepsy to exclude a neoplasm may be indicated.

Isolated Trigeminal Neuropathy: A Report of 16 Cases. J. D. Spillane and C. E. C. Wells. Brain 82:391-416 (Part 3) 1959 [London].

Although isolated lesions of the trigeminal nerve are held to be uncommon, the authors have observed 16 patients with such lesions in the past 7 years. They point out that W. Harris, in his vast experience with trigeminal tic from 1935 to 1950, described 5 cases of neuralgia which was preceded by numbness of the face and trigeminal anesthesia. All the Harris patients had sudden, painless loss of feeling in one side of the face, which after weeks, months, or years was followed by paroxysmal trigeminal pain, similar to trigeminal neuralgia but lacking the characteristic triggers. Harris suggested that the initial lesion was an area of "neuritis" in the trigeminal sensory root, analogous to the lesion of retrobulbar neuritis. The paroxysms of pain did not begin before the facial numbness was regressing: this suggested to him that the pain was caused, in part at least, by stimuli arising distally in the aws and teeth and passing through nerves made bnormally "irritable" by the neuritic process.

The authors think that the site of the lesion of solated trigeminal neuropathy may be at any part f the first sensory neuron of the 5th nerve in its xtrapontine course. The data on the 16 patients re tabulated. In 15 of the 16 patients the predomi- ant lesion was impairment of sensation in the ter- itory of one or more divisions of the trigeminal erve. The course of the disorder tended to be enign. Taste was involved in some cases, and metimes autonomic fibers. In one case there was ophic destruction of the nose, bilateral xeroph- almia, and xerostomia. The histories of this pa- ent and of one other, which was a typical example sensory neuropathy, are presented in detail.

The one patient with involvement of both motor d sensory functions of the left trigeminus was fferent from the others in the series. His initial mptoms which were sensory extended rapidly roughout the territory of the second and third visions on the left, and within a week he was are of impairment of taste and of muscular akness on the same side. Actual muscle wasting s soon evident, and on opening his jaw it devi- ed to the left. When he was admitted to hospital weeks after the onset, the process had already ached its peak, and improvement had begun en he left 3 weeks later. Recovery thereafter s tedious, but was complete within a year. The olution of this illness suggested a virus infection: e patient had no signs of herpes zoster; the ex- sive sensory loss precluded a diagnosis of polio- elitis; and the solitariness of the lesion, together th the normal content of protein in the cerebro- inal fluid, made the Guillain-Barré syndrome im- obable. Similar cases have been reported in the erature under the title of "monoplegia mastica- ia."

Isolated trigeminal neuropathy must be differ- tiated from disorders which may encroach on the sory pathways from the face. Inquiries suggested at cases of similar neuropathy are seen from time time in neurological clinics. Many of them are vestigated as cases of suspected tumor, the nega- e findings on lumbar puncture and radiologic vestigation leading to a "negative" diagnosis. mor of the gasserian ganglion or of the sensory ot or the very rare neurinoma of a peripheral vision and other tumors beginning in or near eckel's cave constitute one of the most important fferential diagnoses of trigeminal pain and sen- ry disturbance.

GYNECOLOGY & OBSTETRICS

Trichomonas Vaginalis Cervicitis and Its Relationship to Cervical Cancer: A Histocytological Study. L. G. Koss and W. H. Wolinska. Cancer 12:1171-1193 (Nov.-Dec.) 1959 [Philadelphia].

During the latter part of 1951 and the first 6 months of 1952, the authors subjected 1,929 female patients of the Strang Cancer Prevention Clinic in New York, who had either a vaginal discharge or a clinically "inflamed" cervix or who showed cytological evidence of inflammation, to a hanging drop examination for the detection of Trichomonas vaginalis. Two hundred twenty-seven (11.7%) of these patients were found to harbor the parasite, whereas 1,702 patients were free of it. Of the 227 patients harboring T. vaginalis, 204 had routine "1-point" biopsies of the cervix. These were taken either from the posterior lip or from areas variously described as showing "erosion" or "redness" or being "iodine negative." Twenty-four of the 204 patients were eliminated from the final study because of insufficient smears or biopsies, and 8 additional patients had significant abnormalities of the cervical epithelium; the remaining 172 patients were available for the basic study of cervicitis due to T. vaginalis. Of the 172 patients, 42 had no follow-up, and 130 were followed up for periods ranging from 1 to 5 years or more, in order to establish the degree of persistence of cytological abnormalities commonly attributed to Trichomonas organisms and especially to see whether any of these inflammatory atypias may conceivably constitute a stage in the development of cervical cancer, as has been advocated by some workers. No routine biopsies were obtained in the 1,702 patients who were free of T. vaginalis; of these, 627 had no follow-up, and the remaining 1,075 patients were followed for periods ranging from 1 to 5 or more years. The purpose of evaluating this group of patients was to determine whether statistically significant differences in the behavior of the cervical epithelium could be established between the patients harboring T. vaginalis and those free of the parasite. All patients in both groups with suspicious results in the cytological examinations had multiple biopsies of the cervix, mainly of the "4-point" type. As additional control, biopsies and smears were examined in a group of 104 patients who were not part of the initial study but who were thought, on clinical grounds, to have some form of cervicitis not associated with T. vaginalis and who were used for comparison of cytological and histological changes with the Trichomonas group. All histological observations were based on the hematoxylin-eosin stain, and all cytological observations on the Papanicolaou stain.

The findings in these 3 groups of patients justified the following conclusions. Cervicitis associated with Trichomonas organisms is characterized by a greater intensity of the inflammatory phenomena than is seen in the absence of these organisms. The inflammatory changes affecting the squamous epithelium of the cervix are especially severe. Extensive vascular participation and considerable epithelial atypia may be observed. With experience, these phenomena may be readily differentiated from disorders with malignant traits, such as dyskaryosis and in situ carcinoma. Bacteriological data indicate that T. vaginalis alone can be implicated as the offending agent. Great caution should be exercised in attempting to estimate estrogenic activity in the presence of cervicitis due to T. vaginalis. Uncomplicated Trichomonas infection, even with severe inflammatory changes, does not warrant any particularly careful cytological follow-up. The incidence of Trichomonas infection *in patients with in situ carcinoma is higher than* the incidence in the population at large. The same is true of other gynecologic disorders and is probably the result of epithelial injury that favors the growth of Trichomonas organisms. The behavior of in situ carcinoma is not predictable, and a biopsy cure occurs in about 10 to 15% of all cases if the patients are kept under uniform conditions of follow-up. The presence or absence of T. vaginalis has no bearing whatever on this behavior. Dyskaryosis, an obscure phenomenon of cell abnormalities bordering on cancer, is observed with approximately the same frequency in the presence as in the absence of T. vaginalis.

The Effect of Pregnancy on Hepatolenticular Degeneration (Wilson's Disease): Report of a Case. J. H. Bihl. Am. J. Obst. & Gynec. 78:1182-1188 (Dec.) 1959 [St. Louis].

The author reports on a 26-year-old woman with advanced hepatolenticular degeneration (Wilson's disease), in whom pregnancy was successfully carried out and terminated with the delivery of a living, normally developed, healthy, full-term male infant. The patient's family history revealed hereditary evidence of Wilson's disease. At the age of 17 the patient noted a tremor of the right hand and speech difficulties; 3 years later she was hospitalized because of abdominal discomfort and dysarthria. At that time the diagnosis of Wilson's disease was established. The patient had previously been treated with chelating agents. During the eventful course of her illness, she had 2 early abortions. Her physical condition at the age of 22 showed some improvement, but her mental condition necessitated commitment to a mental institution. At the time of admission she was pregnant in the first trimester. During the first weeks of pregnancy there was an extensive hyperemesis associated with nephrotoxic signs. On one occasion she became febrile and confused and was treated for impending hepatic coma. Treatment with luteal hormones improved her condition during the latter part of this trimester. The control of her mental condition required the administration of promazine and rauwolfia. She continued to improve and was given leave of absence from the institution.

At the beginning of the third trimester, the patient returned to the hospital with abdominal cramps and low-grade fever. Pus and bacteria were found abundantly in the urine. Typical segmental arteriolar spasms were seen in the fundi of the eyes. In an attempt to consolidate the improvement of the disease, she was continued on a low-sodium diet, and rauwolfia was given to the end of pregnancy. About 4 weeks before delivery the patient developed intense prodromal labor pains with uterine contractions. The pains were more and more accompanied by vomiting and mental confusion, the closer the day of confinement approached. On the 297th day of pregnancy labor began. Uterine inertia was present, but the woman delivered an infant with all signs of maturity, without any developmental or pathological abnormalities, within 10 hours and 45 minutes. There was, however, less vernix caseosa covering the slightly macerated skin, and the subcutaneous turgor was diminished as seen in a stage of dehydration.

The remission of Wilson's disease in this patient continued. The liver impairment receded to subclinical manifestations, and the secondary blood dyscrasia returned to an almost normal pattern. The neurological symptoms, such as tremor dysarthria, and motor incoordination, diminished greatly. The kidney impairment was reversed only to a minor degree. Daily urine copper excretion decreased to normal. Mental symptoms and the Kayser-Fleischer ring remained unchanged. Thus this case shows that nature will take care of itsel in many instances and that pregnancy is a decided blessing in more than one respect.

Pregnancy as a Factor Influencing Relapse in Disseminated Sclerosis. J. H. D. Millar, R. S. Allison E. A. Cheeseman and J. D. Merrett. Brain 82:417 426 (Part 3) 1959 [London].

Inasmuch as the possible association between pregnancy and relapse in women with disseminated (multiple) sclerosis has been discussed repeatedly the authors analyzed the information obtained by 2 of them in a survey in Northern Ireland. The case records compiled by these investigators (Allison and Millar) in 1954 included information about sex, marital condition, age and date of onset, and dates of relapses and pregnancies. A diagnosis of multiple sclerosis was made in 390 women, and in this report the authors are concerned with 26 of these women. Findings suggested that the relapse rate experienced immediately after childbirth was higher than that experienced at other times by single or married women. They raise the possibility of a causal association between childbirth and relapse. The authors discuss 7 factors which suggest 2 possible explanations of the apparent causal connection: 1. Women who have pregnancies tend to date subsequent relapses closer to the childbirth than is true. 2. Women who have pregnancies experience the risks of relapse similar to other women, but, in addition, a relapse may occur earlier.

The authors conclude that there is no evidence of an ultimately worse prognosis in terms of frequency of relapse for childbearing women than for others. Some relapses which would have occurred in women who experience pregnancy are sometimes "anticipated" by the pregnancy. It is suggested that this "anticipation" might be brought about by the stresses of labor and increased work and responsibility of the puerperium, since other stresses, such as trauma, infection, and emotional disturbances, have elsewhere been implicated. With regard to treatment, the authors' studies imply that women with multiple sclerosis should be relieved of as much strain and work during pregnancy, childbirth, and the puerperium as is possible. Severity of relapse or length of subsequent remission was not taken into account in this study, but the authors feel that both of these factors will require investigation.

PEDIATRICS

Myocardial Infarction in the Perinatal Period: Report of Two Cases in Newborn Infants. R. Richart and K. Benirschke. *J. Pediat.* 55:706-712 (Dec.) 1959 [St. Louis].

Two cases of myocardial infarction occurring in the neonatal period are reported. In both instances the delivery was the outcome of an uncomplicated pregnancy; and both infants, born with the cord around the neck, were revived and appeared to be normal at the ensuing physical examination. The first infant, a girl weighing 6 lb. 9 oz. (2,976 Gm.), became cyanotic, although she was placed in 40% oxygen in the nursery. A low-pitched, rumbling, grade 3 systolic murmur was heard over the entire precordium with a maximum at the left sternal border. The second heart sound was inaudible in the aortic area, and the femoral pulses were weak. The electrocardiogram taken at this time was "consistent with congenital heart disease." Despite the intramuscular administration of 0.1 mg. of digitoxin, the infant became progressively cyanotic and died 15 hours and 9 minutes after birth. At autopsy the heart was found to be enlarged, without any other apparent abnormality. An infarction of the tip of a papillary muscle of the mitral valve was found incidentally on microscopic examination. The coincidental occurrence of cyanosis, systolic murmur, and rapid deterioration of the infant appears most consistent with the infarction of a papillary muscle in utero and its rupture shortly after birth. The rupture may have been precipitated by the sudden cardiac stress of extrauterine life.

The second infant, a girl weighing 6 lb. 6 oz. (2,891 Gm.), delivered by low forceps under gas-oxygen-ether anesthesia, progressed satisfactorily during 4 days, then began to have breath-holding spells and became lethargic. A chest roentgenogram showed an enlarged heart, and the electrocardiogram revealed atrial hypertrophy and an interventricular conduction defect. Cyanosis, absence of peripheral pulses, a gallop rhythm, a grade 2 systolic murmur, and an enlarged liver developed in succession, and the infant died at the age of 7 days. At autopsy the only gross abnormality was the heart hypertrophy. In the left ventricle the endocardium had the sclerotic, pale appearance characteristic of subendocardial fibroelastosis. On microscopic examination one small area of myocardial necrosis was found in the right ventricle. Areas of myocardial infarction were scattered over the interventricular septum and on the anterior left ventricle.

The authors believe that myocardial infarctions and coronary artery disease in the neonatal period are more common than is generally known. They emphasize the need for more extensive ante-mortem and postmortem studies regarding the etiology of such pathological changes.

Maternal Influenza and Congenital Deformities: A Prospective Study. V. P. Coffey and W. J. E. Jessop. Lancet 2:935-938 (Nov. 28) 1959 [London].

In an investigation into the incidence of congenital deformities in Dublin carried out in 1955, it was noted that 18.4% of the mothers of abnormal infants gave a history of having had what they termed "influenza" during their pregnancies. When it was predicted that the pandemic of Asian influenza would probably reach Ireland in October-November, 1957, it was decided to use this opportunity to investigate further the possible relation of maternal influenza to fetal deformities. During the 1957-1958 epidemic of Asian influenza in Dublin, 663 pregnant women attending antenatal clinics in the 3 maternity hospitals stated that they had had influenza during their pregnancies. The incidence of congenital deformities in the children born to these women was 2.4 times that in the children of the control group. This is a significant increase. The abnormalities were almost entirely of the central nervous system, and the commonest was anencephaly. The proportion of anencephaly to other abnormalities was about the same in the children of the maternal-influenza group as in the children of the controls. The risk of a malformation was greatest if the infection took place in the first 3 months, and it declined progressively in the 2 subsequent trimesters. There was no significant difference in the incidence of stillbirths and prematurity between the maternal-influenza group and the controls, and the sex ratio of the children was the same in the 2 groups.

Prophylaxis of Rickets in Premature Infants. H. Willi. Helvet. pædiat. acta 14:351-371 (Oct.) 1959 (In German) [Basel, Switzerland].

The author studied clinically, roentgenologically, and chemically 4 different methods of continuous prophylaxis of rickets in 100 premature infants, with a birth weight of 1,500 Gm. (3¼ lb.) or less, in the nursery for suckling infants of the gynecologic clinic of the University of Zurich, Switzerland. Fifty-five infants were given large doses of vitamin D, 15 were given moderate doses of this vitamin, 16 were given small doses of vitamin D and, in addition, calcium biphosphate, and 14 received small doses of vitamin D and, in addition, calcium gluconate or calcium lactate. The food given to these infants consisted mainly of human milk, to which later some buttermilk and nutrient sugar were added. Less failure (27%) of preventing the occurrence of rickets in premature infants was observed with daily doses of vitamin D ranging from 4,000 to 6,000 I. U. than with doses of 1,000 to 2,000 I. U. (53%). The best results, however, were obtained with small doses of vitamin D ranging from 500 to 1,000 I. U. combined with calcium biphosphate (400 to 800 mg. per day). The combination of vitamin D with calcium gluconate or calcium lactate showed the greatest incidence of failure (71%). The results of therapeutic experiments in twins showed particularly well that premature infants fed human milk need, in addition, small doses of vitamin D, calcium, and phosphor to be protected against rickets.

Clinical observations have shown that craniotabes is a less reliable sign of rickets than the thickening of the malleoli. Roentgenograms of the skeleton were of great help in differentiation of rachitic lesions. The author does not share the opinion of other workers that metaphysial osteoporosis of the extremities is to be considered an early sign of rickets. It may often disappear without the occurrence of rickets, and vitamin D does not exert any effect on this osteoporosis, which is related to an insufficient mineralization in the premature infant. It leads shortly after birth to hypocalcemia, which can only be corrected by mobilization of the calcium deposits in the metaphyses.

Surgical Treatment of Atrial Septal Defect in Children. D. C. McGoon, J. W. DuShane and J. W. Kirklin. Pediatrics 24:992-995 (Dec.) 1959 [Springfield, Ill.].

The atrial septal defect is one of those congenital malformations of the heart which, though detectable in childhood, often do not cause significant symptoms until later life. The authors report on 58 children, 15 months to 14 years of age, who were operated on for atrial septal defect, which was not associated with other cardiovascular anomalies, at the Mayo Clinic before December, 1958. Only 3 patients were less than 4 years of age, and 2 of them had more complicated anomalies than had been suspected preoperatively. In 32 of the 58 patients, symptoms or signs noted by the patient or parent could be related to the presence of the defect. Twenty-six patients presented easy fatigability or shortness of breath on exertion, and 10 presented failure to grow and to gain weight properly. Abnormal physical findings consisted of pulmonic systolic murmur in all the patients, prominent overactivity of the heart in 6, wide splitting of the second heart sound in the pulmonary area in all with accentuation of the second pulmonic sound i only 8. Cyanosis was not encountered. On operation the atrial well technique of repair was employed in most instances. In seven cases the technique with use of extracorporeal circulation wa considered necessary; this technique was chose in each instance because other or associated anomalies were suspected. In no case in which the atria well technique was chosen was a condition discovered that was inoperable by this approach. N mortality occurred, and the results were considere excellent in all cases. The authors believe that th repair of an atrial septal defect of significant siz is advisable even in the absence of appreciabl disability. Since there is no urgency for the operation and since conditions are optimal for the operation after the patient is 4 years old, that age shoul be awaited before advising elective operation.

Hiatus Hernia in Infants and Small Children: Report of Observations on 43 Cases. F. Rehbein an W. Hüther. Monatsschr. Kinderh. 107:467-473 (Nov. 1959 (In German) [Berlin].

Reports during the last 3 decades indicate tha hiatus hernia is frequently overlooked in infant and young children. In this report the authors ar chiefly concerned with 3 problems: (1) how to arrive at an early diagnosis; (2) the best method o treatment; and (3) the therapeutic results. The discuss the physiology of the cardia during the ac of swallowing, pointing out that the multiplicity o regulatory mechanisms of the cardia explains tha its function may become readily impaired. The differentiate between sliding hiatus hernias an paraesophageal hernias. Vomiting is usually th first and the most frequent symptom of hiatu hernia. It may appear shortly after birth, and i differs from that observed in the presence of pylorospasm chiefly by the admixture of blood to the vomit. This bleeding is usually caused by a reflu esophagitis, which nearly always develops after the hernia has existed for some time. The bleeding ma lead to hypochromic anemia, and the existence o this form of anemia together with blood-tinged vomit should suggest the possibility of a hiatus hernia. The roentgenologic aspects differ somewhat, depending on whether the hiatus hernia is of the sliding or of the paraesophageal type.

Of the 43 infants and children with hiatus hernia observed by the authors between 1953 and 1958, all but one were operated on. Conservative treatment, consisting chiefly of orthostatic measures to prevent reflux, is suitable only for children with mild forms of hiatus hernia, for while conservative measures may counteract some of the symptoms, particularly vomiting, the hernia and frequently the reflux with its damaging secondary effects may persist. Only 2 of the children operated on had a paraesophageal hernia. Despite the presence of a large hernial sac in both of these cases, no adhesions existed, and so the surgical treatment presented no difficulties. In 13 of the 40 children with typical sliding hernias, roentgenologic changes were already evident on the lower portion of the esophagus, considerable stenosis being present in 8 of these 13. Operation disclosed secondary changes, consisting of indurations of the wall of the esophagus or adhesions, in 11 other children. Only one-third of the children with sliding hernias were free from secondary changes.

With regard to the therapeutic results, the authors say that 34 of the 42 children operated on can be regarded as cured. Six children showed great clinical improvement, but roentgenologic examination still indicated persisting esophageal reflux. Two children died. The authors conclude that early surgical treatment, that is, even during the early months of life, is the best treatment for children with hiatus hernia, because in this way secondary esophageal changes will be prevented.

Prednisone in Childhood Leukemia: Comparison of Interrupted with Continuous Therapy. C. B. Hyman, E. Borda C., C. Brubaker and others. Pediatrics 24:1005-1008 (Dec.) 1959 [Springfield, Ill.].

Thirty children with acute lymphatic leukemia were treated with prednisone, 2.2 mg. per kilogram of body weight per day, for 28 days. After this initial course, they were alternately given interrupted or continuous therapy. In the group receiving the interrupted therapy, the drug was gradually withdrawn over the succeeding 5 to 7 days. In the continuous therapy group, the administration of prednisone was continued, but at a reduced dose of 0.55 mg. per kilogram of body weight per day. Both groups were followed by serial evaluation of the bone marrow, blood, physical findings, and symptoms. The therapy period was considered terminated when relapse occurred, as judged by the bone marrow. The groups did not differ significantly in the number of remissions induced, their duration, or the duration of clinical control. One patient in each group failed to obtain a remission of any degree. These studies do not indicate any advantage for continuous therapy over interrupted therapy with prednisone. On the other hand, with continuous therapy, there are the disadvantages of increased side-effects, higher cost, and the probability of permanent refractoriness to the drug.

THERAPEUTICS

First Clinical Experience with a New Synthetic Antidiabetic Drug, SB 1, or N$_1$-(3-aminobenezene-sulfonyl)-N$_2$-n-butylurea. G. Bickel and O. Koralnik. Schweiz. med. Wchnschr. 89:1186-1191 (Nov. 7) 1959 (In French) [Basel, Switzerland].

Two groups of patients were treated with Sucrida Berna [N$_1$-(3-aminobenezene-sulfonyl)-N$_2$-n-butylurea]. The first group was composed of 13 diabetic patients, between the ages of 60 and 85 years, who also had either another distinct or a complicating disease, such as arteriosclerosis, arterial hypertension, myocardial infarction, and osteitis deformans (Paget's disease). These patients had been hospitalized because of the additional disease. After a preliminary Pfeiffer test they were given Sucrida Berna tablets (50 cg. each) in doses which varied from 2 to 4 tablets daily. Six patients became free from glycosuria and returned to normal glycemia levels with a minimal dose (50 cg. to 1 Gm. daily). Six others required a dosage of 4 tablets daily (2 Gm.) to reach a satisfactory balance. Only one patient with pulmonary tuberculosis failed to benefit from the Sucrida therapy, and responded only to insulin.

The second group was composed of 17 diabetic outpatients without any nutritional deficiency or acidosis, and free from associated diseases. Fourteen of them were between the ages of 40 and 92 years; the other 3 were under 40, the youngest being 26 years old. The duration of the disease varied from 15 months to 22 years. All the patients had been on a diet comparatively low in carbohydrates and fat for several months before starting the therapy; they were kept on this diet except for slight variations. The initial dose of Sucrida was 1 Gm. daily, generally taken in the morning. After 8 days the dosage was reduced or increased as required. Urine and blood examinations were made every 3 days at first, then every week. At the end of a 6-week treatment the results were considered excellent in 10 patients (no glycosuria, or a maximum of 2 Gm. in 24 hours); satisfactory in 4 patients (no glycosuria most of the time, with an occasional increase up to 6 Gm. in 24 hours); moderate in 2 patients (persistent glycosuria, with an occasional increase up to 12 Gm. a day). In one patient the therapy failed to bring any improvement.

The authors believe that Sucrida Berna is an excellent coadjuvant to the dietetic treatment of patients who develop diabetes after the age of 40 and are free from nutritional deficiency and acidosis. In doubtful cases the results can be anticipated by the performance of the Pfeiffer test. Side-reactions are similar to those of carbutamide and tolbutamide, consisting of gastrointestinal irritation or allergic reactions, mostly cutaneous. Unlike carbutamide, Sucrida does not modify the intestinal flora. Sucrida Berna is slightly more active than carbutamide and slightly less active than tolbutamide.

Use of Trimethidinium Methosulfate (A New Ganglionic Blocking Agent) in the Treatment of Hypertension. N. O. Borhani. Ann. Int. Med. 51:983-992 (Nov.) 1959 [Lancaster, Pa.].

Trimethidinium methosulfate (Ostensin) is an asymmetrical bisquaternary amine, possessing ganglionic-blocking properties but demonstrating, in addition, a central component of antihypertensive activity. This paper presents the therapeutic results observed after the oral administration of trimethidinium methosulfate to a group of hypertensive patients; these were selected from a group of patients with severe hypertensive cardiovascular disease, who previously had received one of the ganglionic-blocking drugs presently in use, in combination with other antihypertensive medications, including chlorothiazide. The previous regimen of therapy was withheld, and the oral administration of trimethidinium methosulfate at a dose level ranging from 80 to 240 mg. per day was begun. Patients were given no other medication except digitalis preparations when indicated. The patients were seen in the clinic at 2-week or 3-week intervals.

Of 45 patients treated with trimethidinium methosulfate, 30 have been treated long enough to be evaluated. The drug proved to be a potent ganglionic-blocking agent in most hypertensive patients. It should be used with great caution, because it is unpredictable. When administered by mouth, the dosage should be adjusted according to the patient's response, varying from 80 to 200 mg. a day. The drug should be administered on an empty stomach, and not oftener than twice a day. The side-effects are usually of mild to moderate degree, and may include dryness of the mouth, constipation, blurred vision, and some degree of postural hypotension. The central nervous system manifestations and the severe gastrointestinal complications sometimes seen with the use of other ganglionic-blocking agents did not occur in this clinical trial. Should longer experience with trimethidinium methosulfate confirm this observation, the drug will have merit over other ganglionic-blocking agents presently in use.

Clinical Evaluation of Trimethidinium Methosulfate: A New Ganglioplegic Agent. J. G. Janney Jr., C. Caciolo, G. W. Duane and others. Am. J. Cardiol. 4:745-751 (Dec.) 1959 [New York].

The quest for better hypotensive drugs led to the development of a new ganglionic-blocking compound, trimethidinium methosulfate (Ostensin). This vasodilator drug, which acts through its ganglionic-blocking effect as well as centrally, was tested in 37 patients with hypertension, but the authors evaluated only the 20 patients who were seen at almost weekly intervals. The hypertension was classified as severe in 2, moderate in 15, and mild in 3 of the 20 patients. Most of these patients initially received pentapyrrolidinium, which was gradually replaced by trimethidinium, while other medications were not changed or withdrawn. Trimethidinium methosulfate was given initially in 2 doses of 20 mg. each at 12-hour intervals before the morning and evening meals. Each dose was increased by 5 to 15 mg. weekly, until the level of the blood pressure was reduced to 140/95 mm. Hg, or untoward side-effects limited further increase of the dose. When the total daily dose of trimethidinium methosulfate exceeded 200 mg., the drug was given in 3 divided doses.

Eleven patients experienced an excellent response; 4, a moderate response; 2, a fair response; and 3, a poor response. The duration of trimethidinium methosulfate administration varied from 24 to 48 weeks, with an average of 35 weeks. The average daily dose of trimethidinium was 334 mg., with a range of effective dose of 80 to 780 mg. Those same patients received an average pentapyrrolidinium dose of 533 mg., with a range of 30 to 933 mg. Thus, trimethidinium methosulfate appears approximately one and a half times more potent than pentapyrrolidinium. Of the 15 patients who received pentapyrrolidinium previously, 3 patients had shown an excellent response and continued to do so during trimethidinium methosulfate therapy. Of the 7 patients who had a moderate response to pentapyrrolidinium, 5 had an excellent response to trimethidinium, while 2 were unchanged. Two patients had a fair response to pentapyrrolidinium; on trimethidinium one of these attained a moderate response, and the other remained unchanged. A poor response to pentapyrrolidinium occurred in 3 patients, 1 of whom had an excellent response with trimethidinium, while 2 remained unchanged. Tolerance to trimethidinium methosulfate developed in 2 patients. Two patients with a poor response to trimethidinium achieved an excellent response when other hypotensive drugs were added to their regimens.

Constipation, blurring of vision, weakness, and dizziness were the most common side-effects seen with trimethidinium methosulfate therapy. Comparison of the results obtained with trimethidinium with those reported in the literature for pentapyrrolidinium and mecamylamine showed the control of blood pressure to be at least as good or better and the side-effects to be less severe and more manageable.

RADIOLOGY

Barium Fecaliths Following Gastrointestinal Radiography. A. G. B. Borden and M. B. Hermel. Am. J. Gastroenterol. 32:573-576 (Nov.) 1959 [New York].

The detection of barium fecaliths in the rectosigmoid of 2 patients, in both instances more than one year after barium studies, served as a stimulus for this investigation. One of these patients, a woman of 62 years, had her upper gastrointestinal tract and colon studied because of severe constipation. The other, a woman of 67, had a barium enema examination after colostomy. No laxatives or cleansing enemas were given after those examinations, and no further barium studies were made in the interval. The presence of large semisolid barium sulfate fecaliths was established by radiographic examination of the abdomen, and all were removed by the use of rectal instruments.

One hundred patients undergoing upper gastrointestinal or enema studies with barium were examined at weekly intervals with the purpose of determining the rate of evacuation. Fifty-seven patients examined were free of barium at the end of the first week. The remaining 43 expelled the barium mixture within one month. There was no barium fecalith formation in any of the 100 patients. There was no difference in the rate of expulsion between the orally and the rectally administered barium sulfate mixture. The formation of fecaliths in the 2 aforementioned women patients, more than one year after gastrointestinal studies, most likely represents a rare occurrence. It is, therefore, concluded that in the average patient the formation of fecaliths is most unusual and can be entirely avoided by a careful cleansing of the gastrointestinal tract after barium studies.

Bronchography in Pulmonary Tuberculosis: Clinical Value in 104 Cases. P. Federico, E. G. Espil and others. Prensa méd. argent. 46:1371-1375 (May 29) 1959 (In Spanish) [Buenos Aires].

One hundred four tuberculous patients were subjected to bronchographic examination for diagnostic purposes. The indication for bronchography was confirmation of suspected bronchiectasis in 88 patients, definition of cavities in 58, investigation of suspected cavities in 15, investigation of residual fistulas in 8, and control of the treatment in 11. Fifty-four patients had direct positive sputum for tubercle bacilli. In 111 of the 114 bronchograms taken on these patients, the contrast medium used was propyliodone (Dionosil) in a water suspension, with the addition of carboxymethylcellulose. An anesthetic 0.50% tetracaine solution was used in doses of 4 to 7 cc. Postbronchographic reactions were negligible in 97.5% of the patients; an increase in coughing and expectoration in the few hours subsequent to the examination was considered normal and useful for elimination of part of the contrast medium and its vehicle. Three patients had unfavorable reactions, one of them fatal; the latter was attributed to an excessive amount of contrast medium. The second reaction was attributed to an erroneous evaluation of the patient's condition, and the third had no apparent cause.

Radiologic images of bronchodilatation were found in 89 patients; bronchiectasis had been suspected in 88 of them. Localization of the tuberculous lesions in the upper lobe, parietal retraction (especially surgical), and pleural symphysis were indicated by the lack of opacity in the corresponding pulmonary areas. Bronchographic data did not clarify the investigation and confirmation of cavities and of postoperative residual fistulas. The authors believe that bronchography performed on tuberculous patients with a hydrosoluble contrast medium is a safe diagnostic aid, applicable when the course and the extension of the disease are accurately ascertained. It is the most effective diagnostic device in bronchiectasis associated or not with pulmonary tuberculosis, although it does not indicate the degree of the tuberculous condition in these lesions. It is also useful in indications for collapse therapy and in investigation of mechanical disturbances in the tuberculous and adjacent areas.

Radiation Induced Gastrointestinal Death in the Monkey. S. G. Wilson Jr. Am. J. Path. 35:1233-1247 (Nov.-Dec.) 1959 [Ann Arbor].

Monkeys, free of disease and weighing 5 to 7 lb., were divided into groups and were irradiated. In the radiation facility utilized, 32 radiocobalt (Co^{60}) sources, rated at 237 curies each, were distributed uniformly over a spherical wire frame, 36 in. in diameter. The dose rate in the exposure chamber centered in the sphere was 803 r per minute. Radiation doses ranged from 400 to 40,000 r. An earlier report presented the pathological features in 20 monkeys dying a "central nervous system death." With 2 exceptions, these were animals irradiated with 10,000 r or more. This report is concerned chiefly with 44 monkeys which received between 1,500 and 7,500 r. They exhibited a relatively uniform physical reaction. After the initial episodes of vomiting, diarrhea, nystagmus, and tremors, occurring during and immediately after irradiation, the animals rapidly recovered. By the 5th day after irradiation, however, anorexia and diarrhea reappeared and persisted. Emaciation and dehydration were prominent in all the animals and became more severe the longer the animal survived. In some cases there was as much as a 30 to 35% weight loss by the time of death. The first death occurred on the 4th day, and the last on the 9th day.

The most prominent findings at autopsy were gastric and colonic ulceration. Colonic ulceration occurred in 33 of the animals, and gastric ulceration occurred 13 times. While it is reasonable to assume that an acute dose of 10,000 r of gamma radiation would be at least as efficient as 7,500 r in producing gastric ulceration, it has been observed that animals irradiated with 10,000 r or more die within 3 days and fail to develop ulcers. Therefore, it is concluded that at least 4 days are required for the development of such lesions. After 4 days the incidence of ulceration is a function of dose rather than time. As the total dose is increased, the incidence of gastric ulceration increases. Since gastric ulceration was limited to that portion of the mucosa richest in parietal cells, it appeared probable that selective cell damage was an important factor in regulating the repetitious pattern of the lesions. The predilection of this particular cell for radiation damage was emphasized by the pattern of mucosal atrophy, as found in this experiment as well as in the experiments of others.

Evidence presented suggests that bacteria play a dominant role in the production of gastric and colonic ulceration after supralethal doses of radiation. The severe mucosal atrophy, which occurred in both the small intestine and the colon, could be divided into 4 basic types, which reflected the severity of cytological distortion of the epithelial cells and the degree of epithelial regeneration. In the small intestine the distribution of the lesion types was a function of radiation dose; in the colon the distribution was a function of survival time.

Clinical Experiences with the Effect of Prednisolone on the General Reaction to Irradiation (So-Called Irradiation Hangover), on Hematological Changes Depending on Irradiation, and on Tumor Cachexia. B. Freyer. Strahlentherapie **110:**401-412 (no. 3) 1959 (In German) [Munich, Germany].

The authors report on 50 patients, between the ages of 22 and 86 years, 49 of whom had malignant tumors and 1 had polyarthritis, and who were treated at the Roentgen Irradiation Institute of the City Rudolf Virchow Hospital in Berlin. Forty-three of the 50 patients underwent irradiation therapy, and 7 had tumor cachexia but were not subjected to irradiation treatment. The patients were given prednisolone (Deltacortril), either orally in doses of 5 mg. twice daily or intramuscularly in doses of 10 mg. once daily, for periods ranging from 5 to 80 days. Reactions to irradiation therapy improved quickly after administration of prednisolone. Patients who were given prophylactic treatment with prednisolone before they were subjected to irradiation therapy did not show any significant symptoms of general irradiation reaction. The effect of prednisolone could be substantiated by characteristic hematological changes in 17 of the 43 patients, i. e., by a reduction in the number of eosinophil leukocytes in the peripheral blood, which had shown a marked increase due to the administration of high roentgen-ray doses before the institution of prednisolone therapy. The outstanding effects of prednisolone in patients with tumor cachexia consisted of euphoria, of a favorable influence on the neurological changes caused by tumors or metastases of the central nervous system, and of the possibility (when the administration of prednisolone was combined with that of thyroxin) to produce remissions or to maintain the disease stationary for significant periods in patients with advanced carcinoma of the breast and bone metastases.

The indications for the use of prednisolone therapy in patients with cancer are, therefore, as follows: (1) symptomatic treatment of manifestations of irradiation intolerance and of symptoms of general reactions to irradiation (irradiation hangover); (2) palliative treatment of patients with far-advanced metastasizing tumors and tumor cachexia; and (3) administration of the drug as an adjuvant to patients with neurological secondary manifestations of tumors or metastases of the central nervous system.

The Therapy of Carcinoma of the Eyelid: A Report of 109 Cases. H. Saitmacher and R. Kropp. Strahlentherapie **110:**354-366 (no. 3) 1959 (In German) [Munich, Germany].

Fifty-seven women and 60 men with carcinoma in the areas of the eyelids and of the angle of the eyelids were treated at the irradiation clinic of the University in Marburg on the Lahn, Germany, between 1942 and 1957. The authors report on 109 of these patients, 81 of whom were given primary x-ray short-distance irradiation. The 5-year cure rate was 87.5%. Recurrences of cancer were observed in 16.1% of the patients. Chaoul's short-distance roentgen-ray therapy is the method of choice if the carcinoma is still limited to the eyelid or the canthus. If the tumor has infiltrated bones or orbits, radical surgical intervention and preoperative and postoperative radiotherapy are indicated.

Vertebra Plana (Calvé). W. J. Weston and G. M. Goodson. J. Bone & Joint Surg. **41-B:**477-485 (Aug.) 1959 [London].

The authors describe a case of vertebra plana and present serial radiograms which show the remarkable speed with which the vertebra may collapse and the changes in the pedicles and in one transverse process. A 3-year-old quarter-caste Maori girl was admitted to the Hutt Hospital at Lower Hutt, New Zealand, in May, 1953. She had had several attacks of pain during the 7 days prior to admittance, but apart from these episodes she ran about and played normally. On the day of admission she passed 2 stools consisting of bloody mucus, and acute intussusception was suspected. There was no history of recent injury or infection or of tuberculosis in the family. On examination it was noted that the patient resented being moved. She would lie on her stomach or left side when resting. Radiograms showed loss of the lumbar curve but no other abnormality. During the next days the back pain became worse. There was intense spasm of the posterior spinal muscles, and on attempted movement the child screamed with pain. Further radiograms taken 8 days after the first examination showed collapse of the body of the 5th lumbar vertebra, with increase in the depth of the adjacent spaces. Reexamination a week later showed the body of the 5th lumbar vertebra now as a thin disk. The superior and inferior end-plates appeared intact, and there was a further increase in the depth of the disk spaces above and below the vertebra. There was some loss of bone substance in the pedicles.

Treatment consisted of complete rest on a plaster bed, which relieved the patient immediately from pain. This immobilization was continued for 9 months, after which she was allowed up in a spinal brace. Serial radiograms during this time showed evidence of gradual healing of the lesion, with renewed growth of the vertebral body. The child has been reexamined regularly and has remained free from pain. When she was last seen in October, 1958, the lumbar spine was rather flat, but there was no suggestion of a gibbus. The spine was freely mobile in all directions. The last radiograms showed the body of the affected vertebra to be about half the normal depth. The disk above was of the same height as that between the 4th and 5th lumbar vertebrae, and that below was a little narrower. The anteroposterior diameter of the vertebral body was 40 mm., compared with 28 mm. for the body of the adjacent vertebral body. The progress of the disease in the vertebral pedicles and transverse process in this case is so like that seen in osteochondrosis (Calvé-Perthes disease) of the hip that it is felt that one cause of vertebra plana is aseptic necrosis. Biopsy was not carried out in this patient, and thus the nature of the underlying change could not be determined.

ANESTHESIA

Significance of Electroencephalographic Changes Occurring During Cardiopulmonary Bypass. R. E. Coons, A. S. Keats and D. A. Cooley. Anesthesiology 20:804-810 (Nov.-Dec.) 1959 [Philadelphia].

The authors collected technically adequate electroencephalographic records of 76 successive patients who underwent open cardiotomy with the aid of extracorporeal circulation for surgical correction of congenital or acquired cardiac defects. A bubble-type oxygenator was used, and the perfusion of blood was carried out at low rates ranging from 35 to 50 cc. per kilogram per minute. At the same calculated rates of perfusion, the electroencephalographic pattern remained unchanged in 16 patients, showed initial deterioration followed by recovery during perfusion in 27 patients, and showed changes which progressed to an absence of discernible electroencephalographic activity for periods up to 18 minutes in 33 patients. There were no differences among these 3 patient groups in the rate at which the electroencephalogram returned to its perfusion pattern, or in the degree of awareness shown by these patients in the immediate postoperative period. It is postulated that a level of cerebral perfusion exists, during which encephalographic activity cannot be identified, but during which there is sufficient tissue oxygenation to prevent cellular damage.

It would seem from these observations that the use of a normal electroencephalographic pattern as the criterion for adequate cerebral perfusion and as a guide in the regulation of extracorporeal perfusion rates is neither necessary nor desirable. The authors, however, continue to use the electroencephalogram during clinical anesthesia for open-heart surgery as a sensitive and valuable monitor in determining when hypotension from blood loss, bradycardia, or obstructed circulation has reached dangerous levels.

A Comparison of Ether Anesthesia with Thiopental-Nitrous Oxide-Succinylcholine for Upper Abdominal Surgery. J. P. Bunker, H. H. Bendixen, M. K. Sykes and others. Anesthesiology 20:745-752 (Nov.-Dec.) 1959 [Philadelphia].

The authors report on 693 patients scheduled for elective gastrectomy, cholecystectomy, or common duct exploration at the Massachusetts General Hospital in Boston between February, 1955, and August, 1958. Nineteen (3%) of the 693 patients were excluded, because of severe asthma, pregnancy, or errors in assignment of the anesthetic, and in the remaining 674 a controlled comparison of complications and deaths occurring during and after anesthesia and surgical intervention was carried out. Of these patients, 319 were anesthetized with nitrous oxide, oxygen, and ether, and 355 were anesthetized with thiopental, nitrous oxide, oxygen, and succinylcholine. There was no difference in over-all hospital deaths between the 2 groups. The improvement in operating conditions associated with the use of succinylcholine for relaxation (relaxant technique) was not great enough to cause a detectable diminution in surgical complications, total mortality, length of surgical intervention, or duration of hospitalization.

On the basis of complications directly related to the anesthetic agent, it was not justified to state that one agent or technique was "better" or "worse" than the other. Rather, certain dangers associated with the use of each of the techniques have been identified. Specifically, it appeared that ether anesthesia for upper abdominal operations offered an increased hazard of circulatory depression in the patients of advanced age and in women. On the other hand, the use of light general anesthesia, with succinylcholine for relaxation, appeared to involve, in addition to the obvious dangers of acute hypoventilation in the operative and immediate postoperative period, an increased incidence of the serious postoperative complication of atelectasis, which was greatest in men undergoing gastrectomy.

Hypothermia and Coronary Perfusion for Surgery of Atrial and Valvular Defects. F. J. Colgan, J. A. De Weese, J. A. Manning and E. B. Mahoney. Anesthesiology **20:**811-816 (Nov.-Dec.) 1959 [Philadelphia].

The authors report on 19 consecutive patients with atrial septal defects and 11 with pulmonary valvular stenosis, who underwent open-heart surgery with the aid of hypothermia and coronary perfusion. With a few exceptions, all the patients were premedicated with from 4 to 5 mg. per kilogram of body weight of pentobarbital sodium and 0.01 mg. per kilogram of scopolamine administered intramuscularly 1½ hours before the operation. Cyclopropane was used for inducing anesthesia most frequently in children, and thiopental most commonly in adults. Shortly after induction, electrocardiographic and electroencephalographic leads were attached to the patient. Tracheal intubation was accomplished in a light plane of anesthesia with the aid of succinylcholine. Gas, oxygen, and ether were then employed to maintain anesthesia during the cooling process. The patient was lifted from the operating table and placed in a tub half filled with cold water; he was suspended in the water on a canvas hammock, the cooling being accomplished by adding about 100 lb. of ice cubes. The esophageal temperature, on removal from the ice bath, varied from 31.5 to 33 C (88.6 to 91.4 F). The patient again was placed on the operating table, previously covered with a rubber mattress containing coils through which a liquid could be circulated. This was covered with a bed sheet and a blanket of cotton, on which the patient was placed. The blanket was used to dry the patient thoroughly and was then removed. After removal from the tub, the temperature continued to fall over the next 30 minutes to 1 hour. The average drop was 3.4 C, and the average esophageal temperature at the time of circulatory occlusion was 30 C (86 F).

Before circulatory occlusion, a small dose of a relaxant was given, and the patient was ventilated with 100% oxygen. Blood used for coronary perfusion was collected by the surgeon from the patient's aorta into a heparinized vacuum blood bottle, a few minutes before the vena cava was occluded, the aorta and pulmonary arteries clamped, and the coronary perfusion needle introduced into the base of the aorta. The cardiotomy was then performed, and coronary perfusion was manually controlled by the anesthetist with a commercially available blood administration set incorporating a pressure unit. Perfusion rate was usually from 2 to 3 cc. per kilogram per minute. Blood replacement was no problem. The average amount of citrated blood transfused during the operation was 600 cc. per patient.

Of the 11 patients with pulmonary valvular stenosis, who were subjected to postoperative cardiac catheterization, all showed a reduction of the systolic gradient across the pulmonary valve to an absolute level of 20 mm. Hg or less. All the patients were asymptomatic after the operation and showed major regression of evidences of right ventricular hypertrophy. Of the 19 patients with atrial septal defects, 17 survived, and all had cardiac catheterization as well as clinical evidence of complete closure of their septal defects, with the exception of one patient who showed clinical evidence of a continued left-to-right shunt, which was verified by cardiac catheterization. In the latter the shunt ha been reduced by about 50%, and the patient has had a significant clinical improvement since operation

Hypothermia has proved to be an easily managed and predictable technique. Coronary perfusion with the patient's own arterial blood during th time of occlusion and cardiotomy maintains or restores good myocardial tone and beat. The feasibility of this method of open-heart surgery on th community hospital level has been emphasized.

A Barbiturate Antidote: Use of Methylethylglutarimide in Barbiturate Intoxication and in Terminating Barbiturate Anesthesia. M. J. Marmer. California Med. 91:266-269 (Nov.) 1959 [San Francisco].

Four hundred eighty-eight consecutive patients who were operated on at the Cedars of Lebanon Hospital in Los Angeles were studied in relation to the sleep-reversal stage. The operations varied from a 15-minute-long uterine curettage to an 8-hour-long mastectomy. Only patients anesthetized with thiamylal sodium or succinylcholine or nitrous oxide-oxygen were included in the study. The patients' ages ranged from 7 to 89 years, with most of them in the 20 to 65 age group. Premedication consisted of 25 to 75 mg. of meperidine, or 0.2 to 0.4 mg. of either atropine or scopolamine. The anesthesia was given by the same anesthesiologist to all the patients. Thiamylal was given in doses of 200 to 400 mg. for short procedures, and in twice that amount, or more, for prolonged operations. Succinylcholine was given in a 0.2% continuous drip infusion with constant back titration, and was discontinued soon enough to permit spontaneous return of respiration and of adequate pulmonary ventilation. Nitrous oxide-oxygen was given for analgesia, usually in equal parts and in no instance less than 30% oxygen. Nitrous oxide was withdrawn toward the end of the operation, and the patient was permitted to breathe oxygen only for 3 to 5 minutes. Methylethylglutarimide (Mikedimide) was injected into the rubber tubing, which is part of the infusion apparatus, at the end of the operation in a sterile 0.5% saline solution.

The criteria of arousal were return of corneal reflexes, changes in rate and depth of respiration, movement of the extremities, response to command, and return to consciousness. At the beginning of the study, only 25 mg. of methylethylglutarimide was given to each patient, which proved to be ineffective. A dosage of 50 to 100 mg. was effective in most patients (420); they showed signs of arousal within 1 to 3 minutes after the injection. Sixty-eight patients who had received a dose of 500 to 800 mg. of barbiturate required 150 to 200 mg. of methylethylglutarimide and took 2 to 5 minutes to react. Unfavorable effects were observed in only one patient who developed phlebitis of the forearm. The author concludes that, although methylethylglutarimide is not a specific barbiturate antagonist, it may be considered as a possible antidote. The effect of this drug in stimulating respiration is striking. It reverses the neurological depression resulting from barbiturate anesthesia and the deep levels of narcosis resulting from barbiturate intoxication.

PUBLIC HEALTH

Herpetic Whitlow, a Form of Cross-Infection in Hospitals. H. Stern, S. D. Elek, D. M. Millar and H. F. Anderson. Lancet 2:871-874 (Nov. 21) 1959 [London].

Soon after the establishment of the "septic hand clinic" at St. George's Hospital, London, a relatively high incidence of septic lesions of the fingers was noted among the nursing staff. Altogether 54 cases have been observed, with an average of 3 weeks' loss of work per case. The condition may be a hitherto unrecognized form of hospital cross-infection. All lesions occurred in nurses and affected the digits, the thumb or index finger being most often involved. The whitlow starts as an area of irritation, which soon becomes very painful. It first appears as a deep vesicle, usually near the nail. Soon other vesicles appear, which coalesce, giving rise to a honeycomb appearance. They may remain localized or may spread by crops of fresh vesicles. The process commonly extends under the nail, which becomes separated from its matrix. At a later stage the appearance suggests a whitlow.

In the earlier phases the lesion contains only a little clear fluid, which later becomes turbid; and still later thick yellow necrotic debris, adherent to the underlying true dermis, is found. The small deep vesicles beyond the edge of the lesion establish the diagnosis. The best management is noninterference, treatment being limited to the application of a dry dressing for protection and the prescription of analgesics for the pain. In 7 cases there was a milder recurrence at the original site, from 1 month to 3 years later. It was assumed at first that the lesion was a staphylococcic infection, but, when this could not be proved, and some sterile cultures were obtained in the absence of antibiotic treatment, a viral cause was thought of.

Material for virus isolation was obtained by puncturing an intact vesicle and drawing some of the fluid into a pipette. The material was inoculated immediately into 3 tubes of primary human-amnion-cell monolayers. A cytopathogenic effect characteristic of herpes simplex virus was usually complete within 24 hours. Identification was then carried out by neutralization with high-titer herpes antiserums prepared in rabbits. After virus studies were begun, herpes simplex virus was isolated in 13 of 14 patients with whitlow. Blood was taken from all nurses starting work in the neurosurgical wards; and from those in whom lesions developed, a second specimen of blood was obtained about 2 weeks after the onset of infection. It was thus possible to compare the levels of neutralizing antibodies before and after a lesion. In all but 2 cases no antibody could be detected before the appearance of a lesion; these were primary infections. There was a history of a preceding infection in the 2 cases in which antibodies were present at the onset.

Inquiry about herpetic lesions in the wards revealed 2 possible sources of herpes virus: patients with obvious herpetic lesions, and symptomless salivary carriers. Herpetic whitlow can be readily mistaken for a staphylococcic infection, since it becomes secondarily infected with Staphylococcus pyogenes; but it is not associated with trauma, regional adenitis, or constitutional upset. Herpetic whitlow may be common in hospitals.

Epidemic Rubella in Taiwan, 1957-1958: III. Gamma Globulin in the Prevention of Rubella. J. T. Grayston and R. H. Watten. New England J. Med. 261:1145-1150 (Dec. 3) 1959 [Boston].

Studies of the effectiveness of gamma globulin in the prevention of rubella were carried out in 3 primary-grade schools during a large island-wide epidemic on Taiwan (Formosa). About 1,700 boys from the 3rd to 6th grades, whose average weight was 25 kg. (55½ lb.), were used as subjects. Tests revealed that 5 ml. of gamma globulin, made by 2 different manufacturers, reduced the incidence of rubella by 70%, after those cases occurring during the first week after inoculation had been excluded. Rubella convalescent-phase gamma globulin in doses of 2 ml., however, did not reduce the incidence of the disease; the attack rate among the boys receiving this material was similar to that among the controls who either had received placebos or had had no inoculations at all. The period of protection provided by the commercial-source gamma globulin began 1 week after inoculation and extended for 12 weeks. There was no evidence of modification of the rubella illness occurring in boys who had received this gamma globulin or the convalescent-phase gamma globulin.

Deaths from Asian Influenza Associated with Pregnancy. D. W. Freeman and A. Barno. Am. J. Obst. & Gynec. 78:1172-1175 (Dec.) 1959 [St. Louis].

The authors describe the clinical course and autopsy findings in 11 women, their ages ranging from 19 to 35 years, who died of Asian influenza in association with pregnancy during the epidemic in Minnesota in 1957. Three of the 11 patients were primigravidas, and 8 were multiparas. Three patients died during the second trimester of pregnancy, and 7 during the third; one patient died 5 weeks after childbirth. All 11 patients died of respiratory insufficiency, associated with an overwhelming pulmonary edema and pneumonia. This was demonstrated by clinical and autopsy findings in 9 patients and by clinical evidence in the remaining 2. The patients experienced typical "flu-like" symptoms for from 1 to 10 days before the onset of severe respiratory difficulty. The course was then a fulminant one, characterized by fever, marked respiratory difficulty, cough productive of large volumes of bloody sputum, prostration, and often cyanosis and shock. After the onset of these symptoms, 6 patients died in 24 hours or less, and 2 in 30 hours. There was no evidence that any treatment which was given significantly affected the clinical course. No inoculation with influenza vaccine had been given to 10 of these patients. Autopsy findings revealed pulmonary edema and pneumonia in 9 patients, and gross pulmonary hemorrhage in 7. Hyaline membrane formation was present in 3 patients, and abscess formation in 1. Isolation of the Asian strain, type A, influenza virus from the lung was successful in 3 of the 4 patients in whom it was attempted. Coagulase-positive staphylococci were cultured from the lungs in 2 patients; nonpathogenic bacteria were isolated from pulmonary secretions in 2; and a blood culture in another was sterile. No cultures were taken in the remaining 3 patients.

Reports on the pandemic of Asian influenza indicate that it was the leading cause of maternal mortality in Minnesota in 1957; 50% of deaths among women of childbearing age occurred in pregnant women. Routine vaccination of pregnant women with a suitable influenza vaccine may well be indicated in view of the apparently increased susceptibility of such patients to severe pulmonary complications.

Staphylococci in Cheese: Some Public Health Aspects. F. S. Thatcher, R. D. Comtois, D. Ross and I. E. Erdman. Canad. J. Pub. Health 50:497-503 (Dec.) 1959 [Toronto].

Earlier studies in 1956 in the laboratories of the Food and Drug Directorate, Department of National Health and Welfare, Ottawa, had revealed the common occurrence of toxigenic staphylococci in cheese. Since staphylococcic infections in man and in dairy herds have become increasingly important, and since outbreaks of food poisoning have been traced to cheese, a survey was made during 1957 of the distribution of staphylococci in marketed Canadian cheese made from unpasteurized milk and in cheese imported from several countries, most of which was made from pasteurized milk or subsequently had received bacteriologically equivalent heat-processing. In addition, from a particular factory (factory A), some of whose product had been shown to contain an outstandingly large number of staphylococci, a specimen of milk from each contributing herd was examined for the presence of these organisms, and specimens from 166 different vats of cheese from the same factory were tested for enterotoxin.

Cheese identifiable as to factory of origin and date of manufacture was purchased retail or from packaging establishments with a view to obtaining a representative selection from the main production areas of Canada. Three specimens, providing as wide a range as possible in date of manufacture, were bought from each factory source. For the more intensive examination of cheese from factory A, specimens were obtained to the extent available from each vat of cheese made over a 6-month period. In addition, a 100-ml. specimen of milk was obtained from a single shipping container from each of the 53 "patrons" of the factory.

Of the 149 specimens of cheese from factory A which were tested for enterotoxin, 8 evoked emesis in cats. Control specimens caused no reaction. All toxic specimens were from 30 to 60 days old. Numbers of staphylococci present in the emetic specimens ranged up to 1,500,000 per gram. All staphylococcic strains from emetic specimens were of phage patterns containing 42D in association with other phages. The characteristic type 42D alone was not involved. Thus, the studies showed that coagulase-positive staphylococci are common in Canadian cheese made from unpasteurized milk. The presence of chronic or active mastitis in cattle is considered to be a major contributing factor, as shown by the recovery of the same phage types of staphylococci in cheese as were present, often in very large numbers, in milk from the same sources as used in its manufacture. No staphylococci were found among 236 specimens of imported cheese, made for the most part from pasteurized milk or heat-processed after manufacture.

BOOK REVIEWS

Clinical Auscultation of the Heart. By Samuel A. Levine, M.D., Sc.D., F.A.C.P., and W. Proctor Harvey, M.D., Associate Professor of Medicine, Georgetown University School of Medicine, Washington, D. C. Second edition. Cloth. $11. Pp. 657, with 660 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

This book merits attention, first, because one of the co-authors, Samuel Levine, is a perceptive physician who has devoted a medical lifetime to discovering what he can learn of the heart by seeing, feeling, and hearing what goes on in the precordium and the places in which peripheral vessels may be examined. Second, here is an honest and effective attempt to encourage physicians to use the commonest tool of their trade, the stethoscope, with skill and imagination. Even the modern physicians who will not accept a diagnosis in which laboratory apparatus and technicians are not extensively involved may agree that listening to the heart, if done expertly, will at least give the earliest clue to what further tests are needed.

One might wonder how so large a volume could be written about the limited part of physical examination dealt with here, but when one considers that the authors attempt to give the auscultatory findings of every normal and abnormal condition that affects the heart, the mystery disappears. There is some repetition which tends toward dull and tedious reading, but on the other hand the book contains some "pearls of great price." For instance, the frequently repeated advice to "inch" over the whole precordium when attempting to discover the timing of a murmur or extra sound is valuable. Recognizing the simple fact that the louder of the two sounds heard in the aortic area is the aortic second sound, one can be sure when systole ends. Then as he listens inch by inch down the precordium to hear such things as a gallop, which may not be heard at all at the base, he usually is able to tell whether it is systolic or diastolic in timing.

The scheme throughout the volume is to present electrocardiographic tracings (usually lead 2) synchronized with phonocardiograms so that the sound effects of the events of the cardiac cycle may be correlated with what one hears. Half of the space is filled with these illustrations, and the other half is the written account of what is heard, together with the explanation of the various sounds. The reader apparently is expected to accept the opinions of the authors as gospel as no references are given. Probably no one has listened to or thought about the human heart more diligently than Dr. Levine. Yet, one would think that in dealing with a subject so sharply circumscribed, some of the experimental evidence beyond phonocardiograms might be briefly alluded to. Even an occasional dissenting opinion might be cited so that it could be knocked down.

In the introductory chapter, the authors point out that the phonocardiogram is not necessarily the last resort in deciding whether or not a murmur is present and how important it is, but when the illustrations are completely confined to the scheme described above and the discussions correlated with them, most physicians will come to the conclusion that differences of opinion regarding murmurs can rarely be resolved without such laboratory aid. As the reader goes through this book, he quickly realizes that its maximum usefulness would be attained by having it open at the bedside as he examined normal and diseased hearts, so that the sounds described could be heard and identified at once. Perhaps Drs. Levine and Harvey will some day prepare a set of records of heart sounds with a running commentary in between, such as Bernstein and the other maestros use to initiate the novice into the nuances of fine music.

The use of "auscult" in place of auscultate or listen, and such phrases as "We certainly can not ascribe to the old teachings that a gallop must be above a certain heart rate to be of significance" are unfortunate. It is also regretted that a simple diagram of the heart pointing out where certain murmurs, split sounds, gallops, etc., are heard was not reproduced somewhere in the book. These are minor criticisms. It is a good book for beginner and expert. Every physician who undertakes to give a patient advice about his heart or to treat disorders of that important organ should profit by reading the book.

Dental Roentgenology. By LeRoy M. Ennis, D.D.S., F.D.S., R.C.S., Chairman of Department of Roentgenology, and Professor of Roentgenology, Thomas W. Evans Museum and Institute, School of Dentistry, University of Pennsylvania, Philadelphia, and Harrison M. Berry Jr., D.D.S., M.Sc., Professor of Roentgenology, Thomas W. Evans Museum and Institute, School of Dentistry, University of Pennsylvania. Fifth edition. Cloth. $15. Pp. 607, with 1282 illustrations. Lea & Febiger, Washington Sq., Philadelphia 6, 1959.

This new edition emphasizes clearly the authors' belief that radiodontia is of major importance in diagnosis. The subject matter of this book is well organized and logical in arrangement. The first seven chapters deal with principles of x-ray production and versatility and effective use of x-ray equipment. A description of the important methods and techniques used for making intraoral and extraoral radiographs is included. The effects and dangers of radiation are evaluated in a rational and unemotional manner. Methods are presented for minimizing harmful radiation doses to which patient and operator may be exposed.

The remaining seven chapters cover the area of radiographic interpretation. Radiographic findings of the developmental processes and variations of normal and pathological conditions are well documented with numerous illustrations and precise descriptions. Radiographs showing obscure and unusual conditions are included, and these findings probably represent the most important and valuable material in the book. The authors make little attempt to appraise or evaluate the relationship of oral radiographic findings to systemic disease. Although the discussions are presented from the viewpoint of the dentist, much of the material should be of interest and value to the medical practitioner.

Metabolic Aspects of Renal Function. By William D. Lotspeich, M.D., Professor and Chairman, Department of Physiology, University of Cincinnati College of Medicine, Cincinnati. Cloth. $7.50. Pp. 214, with 58 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This well-written and comprehensive monograph deals with transport of phosphate, amino acid, organic acids and bases in the cells of the renal tubules, and the tricarboxylic acid cycle in the kidney. The chapter dealing with the effects of phlorhizin is excellent. The author assumes a familiarity with basic ideas in cellular metabolism and renal tubular secretion and reabsorption. The kidney is a remarkable organ which excretes almost completely many phenolic substances such as iodine compounds used in urography and found in para-aminohippurate. Since excretion of these involves work, and excretion parallels blood flow, the renal metabolism varies with blood flow. The progress being made in the study of this organ's curious metabolic behavior is concisely described and fully documented in this book.

Water Supply for Rural Areas and Small Communities. By Edmund G. Wagner, Chief Engineer and Associate Chief of Field Party, Division of Health and Sanitation, Institute of Inter-American Affairs, Rio de Janeiro, Brazil, and J. N. Lanoix, Sanitary Engineer, Division of Environmental Sanitation, World Health Organization, Geneva, Switzerland. World Health Organization monograph series no. 42. Cloth. $6.75; 35 shillings; 20 Swiss francs. Pp. 337, with 85 illustrations. World Health Organization, Palais des nations, Geneva, Switzerland; Columbia University Press, International Documents Service, 2960 Broadway, New York 27, 1959.

Fundamental information on acquisition of a water supply has been put together in a brief and practical form for use by people living in small communities located in remote or rural areas of the world. The authors have intentionally omitted many of the complex details usually included in a book on water supply but have listed references for supplemental information. The purpose of the book is not only to stimulate people to initiate their water development programs but also to serve as a pattern by which to carry out such programs. The book accomplishes this purpose.

The first section deals with the planning which must be done by the people in the community who are to direct the development of a water supply program. The socioeconomic and political difficulties which may be encountered are well stated. Methods by which these problems can be avoided or solved are suggested. The diagrams of the various methods of obtaining either surface or underground water by hand or motor driven pumps can be easily understood. Advice concerning the need for training personnel so that there will be proper administrative and functional operation of a water system during the growth of the community is included. The book is a practical handbook and reference book for any physician practicing in an isolated community which does not yet have a municipal water supply.

Recent Advances in Cardiology. By Terence East, M.A., D.M., F.R.C.P., and Curtis Bain, M.C., D.M., F.R.C.P. Fifth edition. Cloth. $10. Pp. 421, with 133 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W. 1, England, 1959.

This new edition is an orderly, thorough, modern, and complete treatise on cardiology. Some chapters may be too complex for men in general practice, but even for them it constitutes a valuable source of widely accepted references. Nothing unorthodox or debatable has been included. It makes good and, as a whole, simple and interesting reading and is recommended without qualification.

Atlas of Rœntgenograpic Positions. Volumes One and Two. By Vinita Merrill. Second edition. Cloth. $32.50. Pp. 291; 295-663, with illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3; Henry Kimpton, 134 Great Portland St., London, W. 1, England, 1959.

The first edition of this work, which appeared in 1949, is recognized as a standard in its field. It might have been more accurate if the publishers had called this recent volume an additional printing rather than a new edition as there have been only minor changes in the text and practically no changes in the illustrations. Anyone owning the first edition would have nothing to gain by purchasing the second. Anyone who does not own the first edition, however, should welcome the opportunity for acquisition which this new printing affords. Most of the text can still be considered up-to-date as there has been little necessity for change in the past 10 years. This is not so in relation to angiographic examinations as here, too, the second edition reprints the original text and illustrations; in 1949, this material, which has as its reference a 1941 publication, was out of date; so, in 1959, it is mainly of historical interest in view of the many developments and accomplishments in this field.

QUESTIONS AND ANSWERS

TERILITY

'o THE EDITOR:—*What diagnostic procedures and treatment can be recommended for a 32-year-old man and his wife who have been married three years and have a sterility problem? The wife has had a complete gynecologic examination which did not indicate any abnormalities. The husband's history and physical examination likewise showed normal findings, and his sperm counts, done on two specimens, were 98,000,000 and 100,000,000 per cubic centimeter respectively. The volume and pH of the samples were normal. Although the morphologic characteristics of the spermatozoa were normal and a testicular biopsy (one side only) showed normal spermatogenesis, all were nonmotile.*

Richard Onofrio, M.D., Los Angeles.

ANSWER.—Total necrospermia in a specimen with count of 100,000,000 spermia per cubic centieter is unusual. It is likely that an error was made the collection of the semen sample through ixture with some chemical substance from a conom, chemical contamination of the receptacle sed for collection, or storage of the sperm at a mperature which was incompatible with their fe span prior to examination. The specimen should e collected in a clean, dry glass jar, stored at a mperature of about 60 to 70 F, and examined ithin one to three hours.

Presumably, the spermatozoa were alive at the rmination of spermatogenesis, in which case a emical alteration in the secretions from the acessory genital glands could kill them; no evidence f this is presented, however. Immobility of sperm ccasionally is due to abnormalities of the centrior bodies and of the caudal extremities, although e sperm heads appear normal. A selective stain hich has a strong affinity for the cytoplasmic omponents of the sperm, such as a 1% aqueous olution of rose bengal, may show structural abormalities. To investigate whether all of the ermatozoa were actually dead one can use a ital red stain or the Blom eosin-nigrosine stain, he latter coloring only the dead sperm.

When sperm motility is less than 30%, fertilizaion of an ovum is not likely to occur, irrespective f the type of therapy given the husband. Since ost of these difficulties are of genetic origin, the dministration of various endocrine substances, inluding thyroid extract or other metabolic stimulators, has no place in the therapy of either male or female sterility of undefined etiology or in a case in which the clinical and laboratory findings fail to signify any significant deficit of the respective hormone.

FIRE ANT STING

To THE EDITOR:—*Is there a new or specific treatment for bites by the fire ant (Solenopsis saevissima richteri)? In my section of Alabama such bites are common, and the patients often have a secondary infection with lymphangitis. Sometimes the lesions become chronic and do not respond to usual measures of treatment. Is the reaction to the bite an allergic phenomenon or due to bacterial invasion?*

Jim S. Phillips, M.D., Butler, Ala.

ANSWER.—The venom of the fire ant is no longer considered to be formic acid, for pure venom is alkaline in reaction and gives a positive nitrogen test result. A crystalline hemolytic principle, with the properties of an amine, which makes up about 90% of the liquid venom, has been isolated.

The ant stings rather than bites, although the mandibles are used to fix its head on the skin. The ant then arches its back at the peduncle and inserts the stinger. It may remove the stinger, and, using the head as a pivot, rotate and reinsert the stinger in two or three additional sites. This clustering of stings is useful in diagnosis. After a victim is stung, a wheal immediately appears in the skin and persists for one hour, regardless of local therapy. Eight to 10 hours later vesicles containing a cloudy fluid, which soon becomes purulent, develop at the puncture site. At this time the vesicles are sterile, but when they rupture, a secondary infection may supervene and cause lymphangitis. An infectious eczematoid dermatitis may develop later, or a more chronic residuum may persist as lichen simplex chronicus.

In addition to the local reactions, the occurrence of febrile or allergic systemic reactions is not infrequent. The fever usually lasts 24 to 48 hours and is rarely more than one to two degrees above normal. The allergic reactions are first manifested by increased local responses in patients to ant stings (larger areas of local edema, erythema, and discomfort); the pustules do not increase in size. Patients may develop generalized urticaria and bronchial asthma shortly after being stung, but more often the victim suffers from a burning sensation, nausea, throbbing in the temples, and apprehension. A few instances of anaphylactic reactions in victims have been recorded.

The answers here published have been prepared by competent auhorities. They do not, however, represent the opinions of any medical r other organization unless specifically so stated in the reply. Anonynous communications cannot be answered. Every letter must contain he writer's name and address, but these will be omitted on request.

There is no satisfactory treatment for the local pustules, which generally clear up in three to seven days. Topical application of steroid, antibiotic, or antihistaminic medicaments is of no value at this time. The allergic reactions are controlled with epinephrine and antihistaminic drugs. Patients can be desensitized against the allergic component of the reaction, but desensitization does not eliminate the formation of vesicles after a sting.

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MINCED SKIN FOR GRAFTING

To the Editor:—*Do you have information on a type of treatment for burns which consists of grafts with finely chopped skin?*

A. A. Linington, M.D.,
Sinoia, Southern Rhodesia.

Answer.—Patients who have been burned through the full thickness of skin pose an urgent and difficult problem, because, while early coverage of the lesion is essential to stop bacterial ingress and fluid loss, donor sites from which autoplastic skin grafts can be obtained may be limited.

Various methods have been advocated for making the available grafts serve a wider area. Thick-split grafts have been cut into small "patch grafts" or "postage-stamp grafts," letting intervening areas fill as the graft extends peripherally. Thick-split grafts can be taken repeatedly and periodically from the same donor area but give slow coverage. Temporary homoplastic grafts have been used for immediate coverage, followed by autoplastic grafts when the homoplastic grafts liquefy and disappear. Skin for grafting has been cut into tiny pieces which, with the use of the blunt end of a straight needle, were then pushed beneath the granulation tissue at an angle.

In 1898 Von Mangoldt scraped donor sites with a razor blade to secure a "pulp" of epidermal cells for grafting. The method in question is a "micro" refinement of the pinch graft, which was widely used at one time. In 1956 Najarian used a sterile kitchen food blender to mince a graft consisting of particles no larger than 10 to 100 cells, which were spread on gauze and then applied to the recipient surface. The results of experimental work performed on rabbits are difficult to interpret, because in these animals the loose skin attachment allows an unusual degree of contraction. Cox and Nichol reported in 1958 that, while this method allows coverage of two and one-half times as much wound area as thick-split grafting, it does not prevent early fluid loss or development of infection. They noted severe wound fixation and contraction, whic resulted in an extremely thin epithelium whic deteriorated when subjected to minor trauma.

References

Najarian, J. S.; Crane, J. T.; and McCorkle, H. J.: E perimental Study of Grafting of Suspension of Skin Pa icles, Surgery **42:**218 (July) 1957.

Cox, W. A., and Nichol, W. W.: Evaluation of Fi particle Skin Autograft Technique, A. M. A. Arch. Su **77:**870 (Dec.) 1958.

RETARDED ENDOCRINE DEVELOPMENT

To the Editor:—*Please recommend treatment fo 12-year-old boy whose testes are palpable times in the scrotum and at others in the ingui canal and are smaller than would be normal his age. Results of tests for 17-ketosteroid a ketogenic steroid levels in this boy are in normal range. The radioiodine* (I^{131}) *concent tion of the thyroid gland was 8% of the d administered and 10% in 24 hours.*

Melvin A. Shiffman, M.D., San Diego, Cali

Answer.—If, in addition to his migratory te (Kunstadter, *J.A.M.A.* 148:117 [Jan. 12] 1952), boy shows other evidence of hypogenitalism and tarded growth in his physical development, de mined by the size of his penis, the presence or sence of pubic hair, and radiographic demonstra of his bone age, he should be given 1,000 IU chorionic gonadotropin intramuscularly three ti weekly for four to six weeks. This usually causes largement and permanent descent of the testes and a generalized spurt of body growth, with appearance of secondary sex characteristics. More than one course may be necessary.

The patient's I^{131} uptake is in the hypothyroid range. The results of such determinations may be influenced by previous ingestion of drugs or foods containing iodine, and this possible source of error must be considered. Determination of his bone age will give some information, but determination of the serum butanol-extractible iodine level is a more reliable test and is not influenced by ingested iodine. If the diagnosis of hypothyroidism is confirmed, thyroid therapy should be given.

RARE DISEASE OF LEUKOCYTES

To the Editor:—*What is Chediak-Higashi disease?*

Stephen Mamick, M.D., Williamson, W. Va.

Answer.—The term Chediak-Higashi refers to an anomaly of leukocytes. Whether the condition is hereditary in nature or a degenerative process due to systemic disease such as lymphoma or leukemia remains undetermined. The characteristic features exhibited by patients with the disease are enlargement of spleen, liver, and lymph nodes, with changes in the leukocytes. The condition occurs rarely, and only a few cases have been reported.

WASHINGTON NEWS

'eport Criticizes Government Medicine . .
pace Medical Office . .
ood Chemicals Law . .
HS on Environmental Health . .
ptometry Bill . .

SPECIAL REPORT RAPS FORAND LEGISLATION

A report on medical care for the aged, compiled y the National Association of Manufacturers, deared that "There is no justification for imposing ı the entire nation a compulsory program that is ınecessary and hazardous."

Proposals in Congress such as the Forand bill to ovide partial financing of some health care needs the elderly through the social security system epresent another stimulus to the ever-increasing ependency of the individual [person] on the fedal government and to the ever-increasing control individual disposable income by Washington," ıe NAM said.

"Voluntary health insurance provides the answer, ıd within a relatively few years all of our senior tizens who want or need such protection will have ," the report noted.

Not only would the measure be unnecessary, the AM said, but it would add to inflation, costing billion dollars a year to start and 7.5 billion dollars year by 1980. Furthermore, "The Forand proosals would not provide care for most people who eed it, since three out of four recipients of Old ge Assistance—the indigent aged—are not OASI eneficiaries nor would they be eligible for benefits."

Meanwhile, Sen. Hubert H. Humphrey (D., Iinn.), a leading candidate for his party's presidenal nomination, renewed his support for Forandpe legislation. In a six-point program for senior itizens, he included a plan to "extend the social ecurity system to cover costs of hospital and nursıg home care for senior citizens." The Forand bill ould also provide payments for surgical services. ınother Democratic presidential hopeful, Sen. John ennedy (D., Mass.), also has sponsored a wide overnment medicine bill.

The Senate subcommittee on aging, the Demoratic majority of which has urged similar legislaion, was slated to start a new round of hearing Iarch 21, with national authorities in the fields of eriatrics and medical economics called to testify.

NEW SPACE MEDICINE DIVISION SET UP

How man can survive in space and whether life exists on other planets were the tasks assigned the ıew Office of Life Sciences of the National Aeronautics and Space Administration (NASA). Named to head the office was Clark T. Randt, M.D., who had formerly been the agency's chief scientist for space medical research.

The office was established as the result of a recommendation by NASA's bioscience advisory committee which said the agency "should undertake a vigorous program in the life sciences as an integral part of the national space program." The committee said NASA should make the fullest possible use of existing aeromedical facilities operated by the military services, while at the same time developing capability for research peculiar to its own programs in manned space flight and basic biological research.

The prime goals of the new division were the biomedical aspects of manned space ventures, fundamental biological problems of space environments, and the search for extraterrestrial life.

Other recommendations of the advisory committee were that (1) the new office be staffed with assistant directors of basic biology, applied medicine and biology, medical and behavioral sciences, and the life sciences extramural program—sponsored research through grants at universities and private facilities as well as at other federal agencies; (2) provisions be made for training and education in the form of training grants, and fellowships; and (3) exchange of information within the scientific community be emphasized.

Dr. Randt, aged 42, earned his medical degree at Western Reserve University in 1943 and joined the medical faculty of that school in 1950 as associate professor of neurology. He later served as director of the division of neurology at the University Hospitals of Cleveland in 1956. He joined the NASA staff last July.

FOOD CHEMICALS LAW GOES INTO EFFECT

A broad law aimed at protecting consumers against harmful chemical additives in food went into effect March 1, but the average consumer will probably notice no difference in the foods he buys.

The law, stemming from a 1959 measure passed by Congress, requires food processors to submit to the Food and Drug Administration proof of the safety of chemicals used to flavor, preserve, or color foodstuffs. Previously, the burden of proof was on the government, which had to go to court to take challenged products off the market. New additives already had been subject to this regulation for a year.

FDA Commissioner George P. Larrick said no widely known food chemical will be banned immediately and that no crackdowns are expected in the near future, although some chemicals used in food may eventually be barred.

(Continued on next page)

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Lown, B., and Levine, S. A.:
Current Concepts in Digitalis Therapy, Boston,
Little, Brown & Company, 1954, p. 23, par. 2.

The law states that chemical additives are to be banned unless they are generally recognized a safe by a large committee of government and pri vate experts established by FDA, or have beer cleared by FDA. The food industry has approve the legislation.

Complete approval has been given by FDA to 3S common substances such as salt and sugar as direc additives in food. Temporary approval—for one yea —has been granted an additional 404 products—13 additives, 202 paper and paperboard materials, an 67 packaging materials. Preliminary tests have ind cated these were not harmful.

The major controversy in regulation of chemic additives has been over an amendment prohibitir use of chemicals that in large quantities may pr duce cancer in test animals or human beings, b that in minute quantities might be absolutely saf The FDA has vigorously supported this amendme on grounds that not enough is known yet about t possibility of cancer danger in human beings fr such sources.

STRONG ATTACK URGED ON ENVIRON MENTAL HEALTH HAZARDS

The Public Health Service called for a unifi coordinated attack on what it described as t growing danger to health from polluted or c taminated air, water, and food.

In a special report on environmental health p pared for the House Appropriations Committ PHS said that for the next 10 years hazards fr the environment can be expected to increase.

The report said there is greater pollution of from chemical sources such as factory smoke a automobile exhaust, in addition to higher levels radioactivity. Knowledge of the effects of low-le radiation is grossly inadequate at the present tir according to PHS.

In some areas chronic bronchitis is becoming increasing cause of disability, the report said, w the rate of occurrence apparently related to clim and to pollution of the air.

"Evidence is also mounting that other dise entities such as lung cancer and emphysema a may be related to air pollution."

About three-fourths of all communities of o 1,000 persons in this country use open dumps other unsatisfactory methods of solid waste dispo contributing to air and water pollution, the rep stated. Use of pesticides on crops and chemi additives in food pose still other new probler

"There are strong indications that unrecogniz occupational factors may contribute to the etiolo of disease now considered solely degenerative origin. Social conditions and strains in the occu tional climate have definite bearing on mental a emotional health.

"Less well understood, but pressing for conside tion, are the health implications of noise, spe pressure, crowding, and associated tensions."

As for water pollution, "Research must be carri out to develop methods of preventing pollution, determine the maximum amounts of polluta tolerable, to find ways of treating harmful bacter agents, or chemical substances in solution.

"The Public Health Service is the logical unit direct an attack on environmental health proble as an interrelated system."

VA OPTOMETRY BILL CLEARED BY HOUSE COMMITTEE

Despite objections by the Veterans Administraion and the American Medical Association, the Iouse Veterans Affairs Committee approved a bill llowing federal compensation of optometrists for utpatient care given veterans with service-conected eye conditions.

In a letter to the Committee, Dr. F. J. L. Blasiname, A. M. A. Executive Vice-president, had said hat "Inasmuch as these activities constitute the ractice of medicine, it is our considered opinion at they should be performed exclusively by qualied doctors of medicine."

In a report on the bill, the Committee said that it xpected the measure would allow VA to "material- expand its use of the services of optometrists in its utpatient fee-basis program. At the same time, the ommittee recognizes that the Veterans Administraon must continue to be vested with discretion to ssure that referrals to optometrists will be made nly where there is reasonable assurance that the rvice-connected medical needs of the veteran are eing fully met."

Noting that the VA had contended that service nnection usually involves a disease or basic defect f the eye and the veteran should therefore have e attention of an ophthalmologist, the Commite said that nevertheless it believes "The services f private optometrists should be more widely sed on a free basis on matters they are qualified handle; namely, refraction and prescription of lasses."

The bill would provide for "very limited applicaon, since the bulk of the operation in this field is on inpatient care basis," the Committee said, noting at the VA predicted the measure, if enacted, vould not produce any substantial increase in the st of the medical program."

Meanwhile, the House passed and sent to the enate a supplemental appropriations bill providing extra $8,800,000 for the VA's inpatient care proram for this fiscal year ending July 1.

MISCELLANY

President Eisenhower had some remarks on the eneral subject of health in his economic report Congress. He said, among other things, "There as been remarkable progress in the reduction of fant and maternal mortality; in the prevention, itigation, and treatment of many diseases; in reoring the physically handicapped; in making vailable a better balanced diet at lower cost; and creating other conditions conducive to longer life nd greater efficiency." At another point, Mr. Eisenower noted that in the past 10 years public and rivate expenditures for health have almost doubled from more than 12 to about 24 billion dollars. nnual federal expenditures for health and medical rograms rose from about 700 million dollars to .5 billion dollars, and state and local expenditures icreased from 1.7 to well over 2.5 billion dollars. The assurance of an adequate supply of doctors nd other health personnel will require an expanion of medical training facilities," said Mr. Eisenower.

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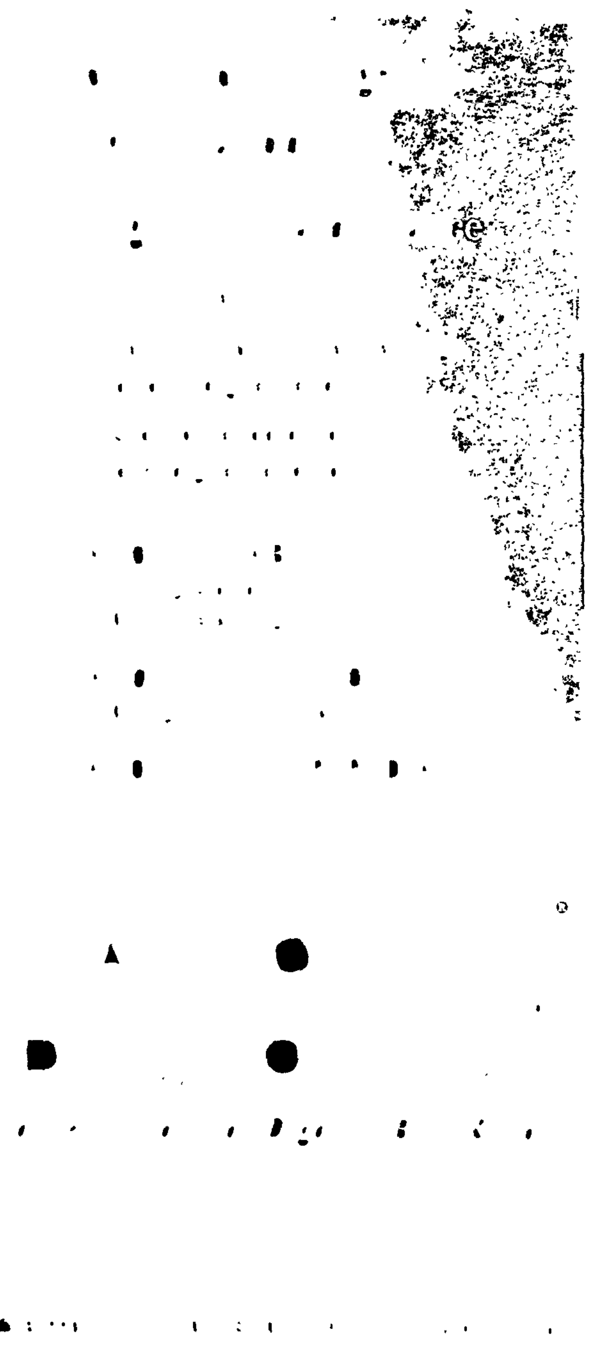

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.

1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 2.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-Dec. 1.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 25-30.

AMERICAN

1960

March

American Academy of General Practice, Philadelphia, Mar. 18-24. Mr. Mac F. Cahal, Volker Blvd., at Brookside, Kansas City 12, Mo., Executive Director.

American Association for the History of Medicine, Inc., Charleston, S. C., Mar. 24-26. John B. Blake, Ph.D., c/o Smithsonian Institution, Washington 25, D. C., Secretary.

American College of Surgeons, Sectional Meeting, The Broadmoor, Colorado Springs, Colo., Mar. 21-23. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Sheraton-Portland Hotel, Portland, Ore., Mar. 28-30. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Gastroenterological Association, Roosevelt Hotel, New Orleans, Mar. 31-Apr. 2. Dr. Wade Volwiler, Dept. of Med., Univ. of Washington, Seattle, Secretary.

American Gastroscopic Society, Roosevelt Hotel, New Orleans, Mar. 30. Dr. Arthur M. Olsen, Mayo Clinic, Rochester, Minn., Secretary-Treasurer.

American Laryngological Association, Deauville Hotel, Miami Beach, Fla., Mar. 18-19. Dr. Lyman Richards, Massachusetts Institute of Technology, Cambridge 39, Mass., Secretary.

American Psychosomatic Society, Sheraton-Mount Royal Hotel, Montreal, Mar. 26-27. Miss Joan K. Erpf, 265 Nassau Rd., Roosevelt, N. Y., Executive Assistant.

American Radium Society, Caribe Hilton Hotel, San Juan, Puerto Rico, Mar. 17-19. Dr. Robert L. Brown, Robert Winship Clinic, Emory University, Atlanta 22, Ga., Secretary.

American Society of Maxillofacial Surgeons, Ambassador Hotel, Los Angeles, Mar. 27-30. Dr. E. M. Collins, Christie Clinic, Champaign, Ill. Public Relations Committee.

Intermountain Pediatric Society, Stardust Hotel, Las Vegas, Nev., Mar. 28-29. Dr. Joseph R. Newton, 2000 S. 9th East, Salt Lake City, Utah, Publicity Chairman.

Neurosurgical Society of America, Del Monte Lodge, Calif., Mar. 30-Apr. 2. Dr. Raymond K. Thompson, 803 Cathedral St., Baltimore 1, Secretary.

Southeastern Surgical Congress, Roosevelt Hotel, New Orleans, Mar. 21-24. Dr. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga., Executive Secretary.

Southwestern Society for Nuclear Medicine, Menger Hotel, San Antonio, Texas, Mar. 26-27. Dr. J. R. Maxfield Jr., 2711 Oak Lawn Ave., Dallas 19, Secretary.

Southwestern Surgical Congress, Riviera Hotel, Las Vegas, Nev., Mar. 28-31. Miss Mary O'Leary, 1213 Medical Arts Bldg., Oklahoma City, Okla., Executive Secretary.

April

Alabama, Medical Association of the State of, Admiral Semmes Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery 4, Executive Secretary.

American Academy of Neurology, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

American Association for the Advancement of Science, Section on Medical Sciences, Vanderbilt University, Apr. 18-19. Dr. George R. Meneely, Vanderbilt University School of Medicine, Nashville 5, Tenn., Chairman.

American Association of Anatomists, Statler-Hilton, New York City, Apr. 11-16. Dr. Louis B. Flexner, Dept. of Anatomy, School of Medicine, Univ. of Pa., Philadelphia 4, Secretary-Treasurer.

American Association of Immunologists, Chicago, Apr. 11-15. Dr. Calderon Howe, Columbia Univ. College of Physicians and Surgeons, New York 22, Secretary-Treasurer.

American Association of Pathologists and Bacteriologists, Hotel Peabody, Memphis, Tenn., Apr. 28-30. Dr. Russell L. Holman, Dept. of Pathology, L. S. U. School of Medicine, New Orleans, La., Secretary.

American Association of Railway Surgeons, Drake Hotel, Chicago, Apr. 7-9. Mr. Chester C. Guy, 5800 Stony Island Ave., Chicago 37, Executive Secretary.

American College Health Association, Toronto, Canada, Apr. 27-30. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary-Treasurer.

American College of Obstetricians and Gynecologists, Netherland Hilton Hotel, Cincinnati, Apr. 2-6. Mr. Donald F. Richardson, 79 W. Monroe St., Chicago 3, Executive Secretary.

American College of Physicians, Mark Hopkins & Fairmont, San cisco, Apr. 4-9. Dr. Edward C. Rosenow Jr., 4200 Pine St., Philad 4, Executive Director.

American College of Surgeons, Sectional Meeting, Hotel Le Minneapolis, Apr. 11-13. For information write: Dr. H. P. S 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Kahler Rochester, Minn., Apr. 14. For information write: Dr. H. P. S 40 E. Erie St., Chicago 11.

American College of Surgeons, West Virginia Chapter, The brier, White Sulphur Springs, W. Va., Apr. 1-2. Dr. Ray E. Grace Hospital, Welch, W. Va., Vice-President.

American Dermatological Association, Inc., Boca Raton Hotel, Raton, Fla., Apr. 8-12. Dr. Wiley M. Sams, 308 Ingraham Bldg., 32, Fla., Secretary.

American Physiological Society, Chicago, Apr. 11-15. Ray G. D D.Sc., 9650 Wisconsin Ave., Washington 14, D. C., Executive Sec

American Proctologic Society, Shamrock Hilton Hotel, Houston, Apr. 25-27. Dr. Norman D. Nigro, 10 Peterboro, Detroit 1, Sec

American Public Health Association, Southern Branch, Me Tenn., Apr. 13-15. Dr. L. M. Graves, Shelby County Health D ment, Memphis, Tenn., Chairman, Local Arrangements Commi

American Society for Artificial Internal Organs, Pick-Ca Hotel, Chicago, Apr. 10-11. Dr. Charles K. Kirby, 3400 Spru Philadelphia 4.

American Society of Biological Chemists, Inc., Chicago, Apr. Dr. Frank W. Putnam, Dept. of Biochemistry, Univ. of Florida, ville, Secretary.

American Society for Experimental Pathology, Pick-Congress Chicago, Apr. 11-15. Dr. J. F. A. McManus, Univ. of Alabam Center, Birmingham, Ala., Executive Secretary.

American Society of Facial Plastic Surgery, Hotel Elysee, Ne City, Apr. 6. Dr. Samuel M. Bloom, 123 E. 83d St., New Y Secretary.

American Society of Internal Medicine, Sheraton-Palace Ho Francisco, Apr. 1-3. Mr. Robert L. Richards, 350 Post St., San F 8, Executive Director.

American Society for Pharmacology and Experimental peutics, Inc., Chicago, Apr. Dr. Karl H. Beyer Jr., Merck Sh Dohme Research Labs., West Point, Pa., Secretary.

American Society for the Study of Sterility, Sheraton-Gibso Cincinnati, Apr. 1-3. Dr. Herbert H. Thomas, 920 S. 19th St., ham 5, Ala., Executive Secretary.

American Surgical Association, The Greenbrier, White Sulphur W. Va., Apr. 3-6. Dr. W. A. Altemeier, Cincinnati General Cincinnati 29, Secretary.

Andrew, John A., Clinical Society, Tuskegee Institute, Apr. 24-29. Dr. Eugene H. Dibble, Memorial Hospital, Tuske tute, Ala., Secretary.

Arkansas Medical Society, Pine Bluff, Apr. 18-20. Mr. Paul C. 218 Kelley Bldg., Fort Smith, Ark., Executive Secretary.

Connecticut State Medical Society, Hamden High School, Apr. 26-28. Dr. William R. Richards, 160 St. Ronan St., Ne Conn., Secretary.

Eastern Psychiatric Research Association, New York Medical School, Alumni Hall "B," New York City, April 7. Dr. Impastato, 40 Fifth Ave., New York City, Secretary-Treasurer.

Florida Medical Association, Robert Meyer Hotel, Jackson 8-12. Mr. W. Harold Parham, 735 Riverside Ave., Jacksonvill Executive Director.

Harvey Cushing Society, Fairmont Hotel, San Francisco, Ap Dr. Edmond J. Morrisey, 450 Sutter St., San Francisco, Ch

Industrial Medical Association, Rochester, N. Y., Apr. 2 Clark D. Bridges, 28 E. Jackson Blvd., Chicago 4, Managing

Iowa State Medical Society, Savery Hotel, Des Moines, Ap Mr. Donald L. Taylor, 529 36th St., Des Moines 12, Iowa, Director.

Maryland, Medical and Chirurgical Faculty of the Stat Alcazar, Baltimore, Apr. 20-22. Mr. John Sargeant, 1211 Cat Baltimore 1, Executive Secretary.

Mid-Central States Orthopaedic Society, Wichita, Kan., Dr. H. O. Marsh, 3244 E. Douglas, Wichita 8, Kan., Secreta

Nebraska State Medical Association, Hotel Cornhusker, April 25-28. Mr. M. C. Smith, 1315 Sharp Building, Lincol Executive Secretary.

North Dakota State Medical Association, Dacotah Hot Forks, Apr. 30-May 3. Mr. Lyle A. Limond, Box 1198, Bisma Executive Secretary.

North Pacific Society of Neurology and Psychiatry, Franklin Hotel, Seattle, Washington, Apr. 8-9. Dr. Thomas H University of Washington, Seattle 5, Secretary-Treasurer.

Society of Head and Neck Surgeons, Sheraton Hotel, Phi Apr. 18-19. Dr. Harry W. Southwick, 30 N. Michigan Ave., C Secretary-Treasurer.

Society of Neurological Surgeons, Olympic Hotel, Seattle, Ap Dr. Guy L. Odom, Duke University Center, Durham, N. C.,

Southeastern Dermatological Association, Nashville, Te 30-May 1. Dr. Robert N. Buchanan Jr., 706 Church St., Tenn., Organizing Physician.

Tennessee State Medical Association, The Maxwell House, Apr. 10-13. Mr. Jack E. Ballentine, 112 Louise Ave., Nashville Executive Director.

Texas Medical Association, Hotel Texas, Fort Worth, Apr. C. Lincoln Williston, 1801 N. Lamar Blvd., Austin, Texas, Secretary.

(Continued on page 26)

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MARCH 19, 1960

MONOVALENT ASIAN INFLUENZA VACCINE

EVALUATION OF ITS USE DURING TWO WAVES OF EPIDEMIC ASIAN INFLUENZA IN PARTLY IMMUNIZED PENITENTIARY POPULATION

H. Bruce Dull, M.D., Atlanta, Ga., Keith E. Jensen, Ph.D., Montgomery, Ala.,
Jennie H. Rakich, R.N., Arthur Cohen, M.S., Donald A. Henderson, M.D.
and
Carl I. Pirkle, M.D., Atlanta, Ga.

The effectiveness of a vaccine against Asian influenza was studied in 1,244 volunteer subjects among the 2,600 men in a prison. Hemagglutination-inhibiting antibodies increased to a maximum within two weeks of vaccination. The titers obtained were highest in the group who received the largest doses of vaccine. Detailed epidemiologic and serologic studies were made during two subsequent waves of epidemic influenza. During the first, vaccines containing 200 and 500 chick cell agglutinating units were about 68% effective, while the vaccine containing 50 CCA units was only about half as effective. During the second wave four months later, all vaccinated men demonstrated nearly equal protection at about the same level observed for the higher doses during the first wave.

IN SEPTEMBER, 1957, a study to determine the protective value of single intramuscular injections of monovalent Asian-strain influenza vaccine was undertaken the United States Penitentiary, Atlanta, Ga. Three ses of vaccine, 50, 200, and 500 chick cell agglu- ation (CCA) units per milliliter, respectively, re compared to a formalinized saline placebo in ms of antigenicity and subsequent protection ainst epidemic Asian influenza.

Six weeks after vaccination of 1,244 inmate vol- teers an epidemic of Asian influenza occurred in penitentiary, concurrent with influenza in the mmunity. Clinical, epidemiologic, and serologic dies demonstrated that vaccine with a potency of 0 or 500 CCA units per milliliter induced 68% otection against febrile influenza, whereas vaccine ntaining 50 CCA units was considerably less ective.

When a second epidemic of Asian influenza swept rough the institution six months after execution of e vaccination program, the vaccine's protection rsisted.

From the Communicable Disease Center, Public Health Service, U. S. Department of Health, Education, and Welfare, and the U. S. Penitentiary. Jensen is now on the staff of the respiratory virus section, Biologics Research Department, Charles Pfizer and Company, Inc., Terre Haute, ; Mr. Cohen is now on the staff of the Department of Statistics, Columbia University, New York.

Material and Methods

The Atlanta penitentiary, a high-security institution, operates with an average inmate population of 2,600 men whose ages range from 18 to more than 75 years, the mean age being 37 years. Housing assignments are most commonly made to cells designed for two to six or more men, although individual units and dormitory arrangements are used in a few areas of the institution. Cafeteria procedure and occupational and recreational programs permit relative freedom of movement, intermixing, and personal contact. Medical care is centralized in a well-staffed hospital and an outpatient clinic.

All inmates were invited to volunteer for participation in the vaccine study by general announcement; the only contraindication to acceptance was known allergy to eggs or egg products. On Sept. 4 and 5, 1,244 volunteers were registered and assigned in rotation to receive one of the three doses of Asian-strain-influenza vaccine or a placebo. All four injections were 1 ml. in volume and identified only by code.

TABLE 1.—*Percentage of Penitentiary Inmates with HI Antibodies Two Weeks, Four Weeks, and Six Months After Administration of One of Three Doses of Monovalent Asian-Strain-Influenza Vaccine or Saline Placebo*

	Interval								
	2 Wk. Titer†			4 Wk. Titer†				6 Mo.* Titer†	
		%, Positive	Geometric Mean	No. Tested	%, Positive	Geometric Mean	No. Tested	%, Positive	Geometric Mean
Placebo	61	2	..	59	2	..	67	3	1
50 CCA Units	61	56	13	59	54	11	66	9	2
200 CCA Units	63	75	36	63	64	22	64	22	2
500 CCA Units	60	90	85	56	82	50	65	19	2

* Different, randomly selected sample of men bled at six months.

† Positive with initial dilution of 1:20 or greater (all prevaccination serums zero antibodies). Titers less than 1:20 treated as titers of one.

To evaluate the antibody responses stimulated by the vaccine, every fifth man registered (20% of each group) had one blood sample collected prior to injection and was scheduled for collection of additional specimens two and four weeks later. Six months after vaccination (preceding the second outbreak of respiratory disease), serums were again obtained to determine antibody persistence. Although the same men had contributed samples for the two-week and four-week tests, a different 20% of subjects was randomly selected for the six-month collections to equalize the obligations of all volunteers somewhat. Clinical histories were obtained from the subjects at the six-month bleeding time to achieve a more accurate evaluation of serologic evidence of intercurrent influenza infection, particularly in those men who had received placebo.

Daily observations were made of all respiratory illnesses reported either in the penitentiary's regular medical "sick line" or as emergencies. Clinical history, physical findings, and pertinent epidemiologi data were routinely ascertained in each instance Beginning in late October, 1957, when the increase incidence of respiratory illness suggested th *incipience of an epidemic* outbreak, about 2 throat washings were obtained for virus isolatio and serum specimens, in the acute phase and du ing the two-to-three-week period of convalescenc were collected from all patients with respirato illness, both afebrile and febrile, that occurred the population under study. Physicians and nurs from the Communicable Disease Center work daily with the prison medical staff, interviewing patients and organizing records and collection specimens. By early December the outbreak h subsided, and routine daily surveillance was c continued.

A second wave of the epidemic occurred March, 1958, four months after the first. Methods study were more limited in this instance and cluded only collection of throat washings fr about 12 patients and review of all clinic visits a hospital admissions. Thus, in the first wave, di nosis of influenza was based on clinical findi that had been confirmed by virological and se logic study. In the second wave, diagnosis limited to evaluation of the incidence of feb illness during an outbreak of respiratory dise when the Asian influenza virus was prevalent.

The vaccine was an aqueous-type material c taining only formalin inactivated A2/Japan/305 influenza virus and was obtained for this through the Division of Biologics Standards of National Institutes of Health. The stock vacc contained 500 CCA units per milliliter, and other doses were prepared by its dilution with ste isotonic sodium chloride solution. The placebo c tained isotonic sodium chloride solution, formalin, and 1:10,000 thimerosal (Merthiol solution—the latter two compounds being in same concentrations as in the 500 CCA-units cine.

Hemagglutination-inhibition (HI) tests w conducted with serial dilutions of serum and hemagglutinating units of virus in a standa pattern test.[1] The A2/Japan/305/57 strain, wh had been transferred serially in eggs, ferrets, m and eggs, was used to provide an antibody-sensi virus. Serums were treated with potassium perioc to destroy nonspecific inhibitors.[2]

The complement-fixation (CF) technique use standard overnight fixation at a temperature of with two optimal units of the same virus strain infected allantoic fluid as the antigen.[2b]

Results

Vaccine as Antigen.—The relationship of antibody response to vaccine dose is presentec table 1 and figure 1. In general, it was observed the development of antibodies after vaccinat with Asian influenza vaccine was directly related to the dose given. HI antibodies increased to peak levels within two weeks of vaccination and declined considerably thereafter to relatively low levels six months later.

Table 1, which summarizes antibody responses two weeks, four weeks, and six months after vaccination, shows the percentage of each group of vaccinees who developed significant rises in titer (fourfold or greater) and lists the corresponding geometric mean titer for each group. While only 56% of the men who had received 50 CCA units of vaccine demonstrated rises in antibody titer two weeks after vaccination, the groups of men given 200 or 500 CCA units, respectively, showed a considerably greater response, that is, 75 and 90% respectively. Serums collected six months after vaccination revealed a marked decline in antibodies among all groups, indicated by both decreasing geometric mean titers and reduction in the proportion of men with antibodies. Fig. 1, which shows the percentage of each group with antibodies two and four weeks after vaccination, emphasizes the direct relationship of response to vaccine dose.

According to the HI titers shown in table 1, few, if any, inapparent Asian influenza infections appear to have occurred between the time of vaccination and the collection of a blood specimen six months thereafter. The virtual absence of antibodies in the group of men given placebo, and the fourfold decrease in the percentage of men with antibody titers in the three vaccinated groups would not be expected had there been a high rate of infection. Only two persons in the group given placebo demonstrated antibody titers at six months, and single positive reactions had also been noted in both of the previous collections, from a different person in each instance. If subclinical infections had occurred, a significantly greater number of serologically identified cases should have appeared in the group given placebo, and the antibody levels of the vaccinated groups should have been maintained.

To describe more accurately and completely the immune status of each group of volunteers given vaccine, the distribution of HI antibody titers two weeks after vaccination was analyzed on the basis of the cumulative percentage of each group with titers equal to or greater than 1:20, 1:40, 1:160, and 1:640 dilutions of serum. The more concentrated doses produced higher titers throughout the range of serum dilutions.

The Two Waves of Epidemic Influenza.—An epidemic of Asian influenza broke out in Atlanta in late October: Public-school absenteeism showed a fourfold increase; the Georgia Institute of Technology housed the overflow of its ill students in the Naval Armory; Atlanta hospitals reported a sometimes overwhelming increase in outpatient-clinic and emergency-room visits; and Atlanta's influenza-pneumonia mortality increased more than eightfold, reaching its peak in early November. Asian influenza virus was repeatedly isolated in throat washings collected from patients who were ill at various times during the course of the community-wide epidemic.

Coincident with the outbreak of influenza in Atlanta, the penitentiary population experienced a sudden increase in both afebrile and febrile respiratory disease. Daily sick lines were crowded by men reporting a variety of complaints, and the number of emergency medical visits increased rapidly. Febrile cases constituted about one-third of the total and, as will be demonstrated later, accounted for the greatest proportion of serologically confirmed infections. From the perspective of subsequent evaluation, afebrile patients probably had cases of either nonspecific illnesses or "goldbricking," a phenomenon well recognized in institutionalized populations.

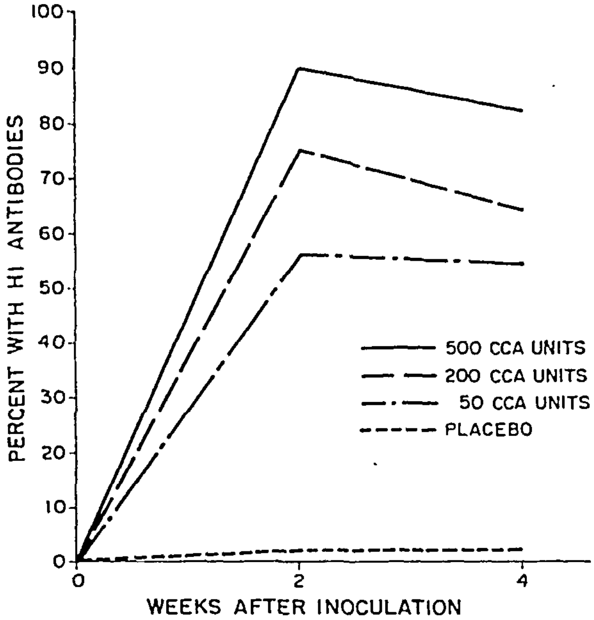

Fig. 1.—Percentage of inmates of U. S. Penitentiary, Atlanta, Ga., with hemagglutination-inhibition (HI) antibodies two and four weeks after inoculation of one of three doses of monovalent Asian-strain-influenza vaccine or saline placebo.

Fig. 2 shows the incidence of respiratory illness in the penitentiary by week during the six-month period after the vaccination program. Two major increases in the amount of reported illness are evident, the first beginning in late October, the second occurring in March. Both waves are compared to the influenza-pneumonia mortality reported in Atlanta for the corresponding weeks. In addition, pertinent newspaper excerpts describing the widespread epidemic that occurred in schools in the area in the autumn have been added for comparison with the penitentiary's first wave of respiratory illness. The peak incidence of illness at the penitentiary in the fall occurred one week prior to the maximum level of mortality reached in Atlanta and coincided with school-wide epidemics.

On the basis of the epidemic curve, the interval from Oct. 26 through Nov. 20 was designated as the "autumn epidemic study period" for evaluating vaccine effectiveness. During these 26 days, 455 men reported respiratory illnesses—189 from the population under study. Sixteen men were hospitalized because of unusually severe illnesses, some of which were complicated by bacterial pneumonia. Only one of the hospitalized inmates had taken part in the vaccination program, and he had received placebo.

The men's illnesses varied considerably in severity. Symptoms reported by a large number of inmates were those of classic influenza: abrupt onset of shaking chills, generalized myalgia, headache, fever, malaise, anorexia, and variable upper respiratory symptoms including coryza, sore throat, and nonproductive cough. The condition of afebrile patients, those having temperatures of less than 100 F (37.8 C), was characterized mainly by malaise, anorexia, and an occasional complaint of feverishness.

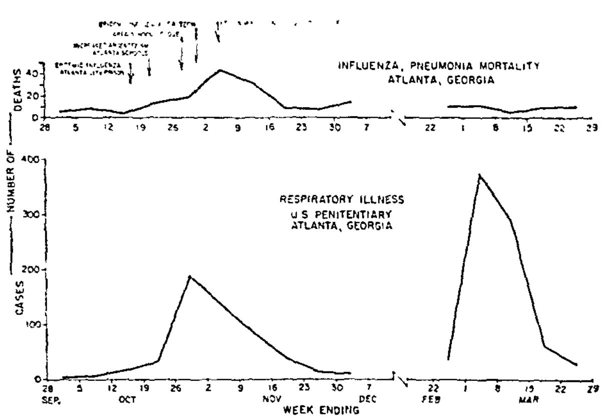

Fig. 2.—Incidence of respiratory illness among penitentiary inmates by week during six-month period after vaccination against Asian influenza, and comparison with influenza-pneumonia mortality during concurrent influenza epidemic in Atlanta community.

Throat washings for virus studies were collected from 23 men, mostly from those with febrile illnesses occurring at the peak of the outbreak. Virus was isolated from 11 of the 23 specimens (48%), 10 of these being from febrile patients. All of these isolates were identified as Asian-strain-influenza virus.

Comparison of focal epidemics in the institution's nine major housing units demonstrated that the earliest outbreak occurred among men in the administrative orientation (A/O) group, which is composed of newly admitted inmates. These men are housed separately from the others for a period of one month while undergoing tests and observation. Four to five men enter the administrati orientation unit daily, and a similar number is leased for assignment to one of the permanent livi areas. The early focal outbreak in this particu group suggests that new arrivals may well ha introduced the Asian-influenza virus and that m discharged from the administrative orientation a then seeded it widely in the general inmate popu tion. Influenza occurred among the several hund guards and other personnel employed by the pe tentiary simultaneously with most of the outbre among inmates. Having contact with both inma and the Atlanta community, employees may have contributed to dispersion of Asian-influe virus in the institution.

In March, 1958, six months after the vaccina program had been completed, an explosive sec epidemic of respiratory disease swept through institution. In late February only 5 to 10 illne had been reported daily, nearly all of them afeb During the first week of March the number creased dramatically to nearly 100 new cases day, almost half of the patients having a temp ture of 100 F or more. The acuteness of the break is illustrated in fig. 2. It is of interest to that no indicators of an epidemic in the Atl community coincided with the penitentiary's ond wave of respiratory disease: the city's i enza-pneumonia mortality remained at seas levels, and school absenteeism did not increase

During the 15 days arbitrarily chosen as "winter epidemic study period," March 3 to M 17, a total of 689 inmates reported a respira illness, 269 of whom were from the popula under study. Symptomatically, the illnesses identical to those which had occurred in the Once again, however, a broad spectrum was served. Fourteen throat washings collected febrile patients early in the course of the epid yielded eight viral agents (57%), all of which identified as Asian-strain influenza.

Effectiveness of the Vaccine.—Although the cine proved to be about equally effective du both actual outbreaks of respiratory illness, i esting variations in HI antibody levels occurre the interval.

During the first wave a total of 189 case respiratory illness occurred in the population u study. Satisfactory serum specimens were obtai during both the acute and the convalescent p and then tested on 166 (88%) of these pati Laboratory confirmation of infection was def as a fourfold or greater rise in antibody levels the acute-phase to the convalescent-phase sp mens, as demonstrated by either HI or complem fixation tests.

Table 2 presents results of the 166 serologic in relationship to the maximum body tempera developed in the patients. Three tempera oups, equal to or lower than 99 F (37.22 C), 2-99.8 F (37.33-37.66 C), and equal to or higher n 100 F were selected to represent afebrile, ermediate, and febrile classifications. Such a ouping of results demonstrates the definite relionship of serologic confirmation of infection to e presence of fever.

While of 42 patients with temperatures of 100 F more 71% (30 of 42) had Asian influenza, only % (7 of 33) with an intermediate temperature crease and 4% (4 of 91) of the afebrile patients d confirmed cases. Thus, a body temperature of 0 F or more proved to be a reliable criterion for e diagnosis of Asian influenza in the first wave, nsidering that nearly three-quarters of all patients th confirmed cases (30 of 41) had such elevations temperature. Twenty-seven of the total of 41 nfirmations (65%) were made by HI tests, 37 %) by complement-fixation tests, and 18 (44%) by th procedures. Because the illnesses of a large mber of men could not be confirmed as Asian luenza, additional serologic studies were underen. Tests with adenovirus and influenza type-B tigens were performed but were uniformly negae.

In view of the direct relationship between fever d serologic confirmation of actual infection, an alysis of the effectiveness of vaccine in prevent; febrile illness was carried out. While the ount of afebrile illness remained relatively connt, the number of patients with a fever of 100 grees or more decreased progressively from 19 in group given placebo (7% of that group) to 12 %) of the group given 50 CCA units of vaccine, d to only 6 (2%) each in the groups vaccinated th 200 CCA and 500 CCA units respectively. Statical analysis at a significance level of 0.05 suprts actual differences in the incidence of febrile ness in relation to placebo. Effectiveness of the ccine in terms of percentage reduction in febrile ness is 38% for 50 CCA units of vaccine and 68% r both 200 CCA and 500 CCA units of vaccine.

An additional evaluation of the effectiveness of e vaccine was made by studying only the laborary-confirmed cases (table 2). Among the total of confirmations, 20 were in the group of subjects ven placebo, 13 were in the group given 50 CCA its of vaccine, and only 3 and 5, respectively, ere in the groups given 200 CCA and 500 CCA its. Because of the small number of confirmed fections in the last two groups, the groups have en combined for analysis at a significance level 0.05. Effectiveness levels are quite similar to ose calculated when the vaccine is considered om the standpoint of protection against febrile lness: 37% for 50 CCA units of vaccine and 75% r 200 CCA and 500 CCA units of vaccine comined.

The immunity of the vaccinated inmates can be further defined. The HI titers of all acute-phase serums that had been collected during the epidemic (166) were grouped according to the vaccine dose received and related to the presence or absence of fever. As might be anticipated, all acute-phase HI titers in the group given placebo were zero, while the vaccinated groups showed a distribution of titers ordered according to vaccine dose. However, within the vaccinated groups it was generally apparent that febrile patients had many more zero or low antibody titers than afebrile ones. Although the number of cases in the groups given 200 CCA and 500 CCA units of vaccine, respectively, is too small to allow completely adequate analysis, the results suggest that the presence of HI antibodies at the time of infection is directly related to protection against developing febrile illness. Moreover, it appears that the relative antibody level is more important than the mere presence or absence of antibodies.

TABLE 2.—*Autumn Outbreak of Respiratory Illness at Atlanta Penitentiary, October, 1957: Relationship of Serologic Confirmation* of Asian Influenza to Occurrence of Fever*

	Maximum Recorded Temperature								
	≤99F		99.2-99.8F		≥100F				
Vaccine Group	Tested	Confirmed	Tested	Confirmed	Tested	Confirmed	Total Tested	Total Confirmed	% Confirmed
Placebo	19	1	8	2	19	17	46	20	43
50 CCA units	26	1	8	3	12	9	46	13	28
200 CCA units	23	0	6	1	6	2	35	3	9
500 CCA units	23	2	11	1	5	2	39	5	13
Total	91	4	33	7	42	30	166	41	25
% confirmed	4		21		71		25		

* Confirmation defined as four-fold or greater rise in HI or CF antibody titers from acute-phase to convalescent-phase serums.

When the second wave of respiratory illness occurred at the Atlanta Penitentiary in March, only 844 of the original 1,244 volunteers were still in the penitentiary, reflecting the more than 30% turnover in the inmate population. During the period of this study, March 3 to March 17, a total of [illegible] respiratory illnesses were reported, 269 ([illegible]) from the group under study.

As anticipated, some of the men reporting an illness in the winter outbreak were also among those who had been ill during the first wave of influenza. It appeared that, of the 269 men who were ill in the winter, 61 (23%) reported illnesses in both outbreaks. What is of interest, however, is the observation that more than 80% of the men who had also been ill in the fall had then been afebrile. Occurrence of febrile illness in both outbreaks was noted in only five instances. (Three of these five men had been confirmed serologically as Asian influenza in the fall, but, because much of the study in the second wave was retrospective, laboratory confirmation was not possible.)

Fever having been shown to be a reliable criterion for confirmation of influenza during the first wave, the occurrence of febrile illnesses among the vaccinated men in the winter outbreak was studied to determine the persistence of protection given by the vaccine. Since 61 of the 269 patients who were considered ill in the winter outbreak had also been ill in the fall, a comparative analysis was made of the cases that occurred exclusively in the winter with the total number. While there were about equal numbers of afebrile illnesses in all groups, there were considerably fewer febrile cases in the vaccinated groups than in the groups given placebo, namely, 19% in the group given placebo but only 8, 7, and 7%, respectively, in the groups that had been given 50 CCA, 200 CCA, and 500 CCA units of vaccine.

The percentage effectiveness of each vaccine dose in preventing febrile illness, based either on winter outbreak cases exclusively or on totals (the latter results being parenthesized), was as follows: 50-CCA-unit vaccine, 60% (50%); 200-CCA-unit vaccine, 62% (63%); and 500-CCA-unit vaccine, 65% (58%). Similar measures of effectiveness were observed (irrespective of whether men who had been ill in both epidemics were included in the analysis). It is of considerable interest to compare the evident protection conferred by the vaccine in the winter to that observed in the autumn. With the exception of the 50-CCA-unit dose, the level of protection in both epidemics was about the same. In the fall the 50-CCA-unit vaccine was considerably less effective than the higher doses, but in the winter it appeared to be of nearly equal value. An immunological explanation of this observation will be suggested later.

Comment

During the past 15 years considerable data on influenza, its clinical, epidemiologic, and laboratory characteristics have been accumulated.[3] Emergence of the Asian variant in 1957[4] presented a unique opportunity for additional investigations. A large portion of the resultant work has dealt with the antigenic character of the virus and the protective value of Asian-strain-influenza vaccines tested under a variety of conditions.[5]

Reports of studies sponsored by the commission on influenza of the Armed Forces Epidemiological Board demonstrated a 42 to 75% reduction in relative rates of respiratory diseases, depending on vaccine dose and the particular conditions of the study. Investigations by the U. S. Public Health Service and a number of clinical and university centers have produced comparable results. The present study, conducted under institutional conditions, demonstrates similar patterns in terms of the vaccine's antigenic character and its protective val
Certain of the procedures, observations, and resu
in the present study deserve additional comm
and discussion.

The accessibility of a penitentiary population
virtue of its routine living and medical progr
favors the choice of such a group for clinical stu
However, these rather obvious benefits are o
accompanied by errors due to overreporting of
ness, or "goldbricking," which occurs in instituti
in which special consideration is available to
sick. Another inaccuracy is underreporting,
counted for by a segment of inmate populat
which is described as refusing medical care
evidence of their resistance to authority. The m
nitude of the reporting errors on either count
not be satisfactorily estimated, but the existenc
inaccuracies must be taken into account in
evaluation of the results of clinical studies. S
definition of a "case" needs, therefore, to be es
lished and respected.

To minimize the anticipated errors in diagn
of influenza, with awareness of both its inhe
clinical variability and the likelihood of repor
errors, fever as the criterion was adopted as
best objective clinical index of infection. On
basis of reasonable confidence in consistent
nosis, the cases of illness established by this
of clinical screening provided a sample in w
to measure and compare the protection afforde
the vaccine.

Considerable support was added to fever as
diagnostic criterion by showing that in nearly th
fourths of the patients with temperatures of 1
(37.78 C) or more Asian influenza infection c
be confirmed serologically while afebrile illn
were rarely confirmed (table 2). On the basis of
evidence, which had been accumulated during
first wave of respiratory illness at the Atlanta P
tentiary, fever was used as the sole criterio
infection during the winter outbreak.

In both waves of respiratory illness most of
patients were essentially afebrile. Although
tempting to explain this observation in term
mild or modified influenza, the paucity of case
laboratory-confirmed infection in afebrile pati
offers little support for such a thesis. It is n
reasonable to consider the afebrile illnesses
occurred among the penitentiary inmates as
specific infections or "goldbricking," which occu
in an epidemic pattern and were superimposed
the actual outbreaks of Asian influenza.

In the autumn, the stimulation of antibody
duction by the Asian-influenza vaccine was
served to correlate with the administered d
Furthermore, there appeared to be a definite

tionship between the level of HI antibodies and he protection given by the vaccine against devel- ping a febrile illness. In the winter, however, the rum specimens that had been collected shortly efore the epidemic demonstrated a marked decline HI antibodies. During the actual outbreak, how- ver, it was observed that all vaccinated men were rotected to about the same degree as in the fall, gardless of whether they had received high or w doses of vaccine.

There may be merit in attempting to explain this pparent paradox in terms of possible immunologi- l mechanisms: In the autumn, the interval be- veen vaccination and the actual epidemic (six eeks) may not have been sufficiently great to low for anamnestic mechanisms to stimulate in- eased antibody production when virus activity gan, and the protection obtained was therefore osely correlated with existing serum-antibody vels. The fact that acute-phase titers among brile patients generally were lower than among ebrile ones adds support to this hypothesis. In ntrast, six months after vaccination, nearly all en in the vaccinated groups had lost most of their culating antibodies. However, the timing was ch that a small amount of antigen was sufficient produce a rapid booster effect in the form of an amnestic recall, thus giving comparable protec- n among all men previously vaccinated.

Summary

Three doses of monovalent Asian-strain-influenza ccine, containing 50, 200, and 500 chick cell glutination (CCA) units, respectively, were com- red to a saline placebo for evidence of antigenic- and protection against epidemic Asian influenza. ngle, intramuscular injections of vaccine were ministered to 1,244 volunteers among nearly 300 inmates of the federal penitentiary in Atlanta, ., in the autumn of 1957. Two outbreaks of spiratory illness, in part Asian influenza, occurred intervals of about six weeks and six months, spectively, after the vaccination program.

The conclusions based on clinical epidemiologic d serologic studies are as follows: 1. The vaccine mulated serum hemagglutination-inhibition(HI)- tibody production in correlation with the dose ministered. Two weeks after vaccination, 56 to % of vaccinated men demonstrated antibody ers. Six months later, there had been a consider- le decline in antibodies among all three groups vaccinees. 2. During the first wave of respiratory ness, a correlation of nearly 75% was observed tween patients with a temperature of 100 F 7.8 C) or more and subsequent serologic confir- ation of Asian-influenza infection; afebrile ill- sses were confirmed infrequently. 3. The vaccine's protection against developing febrile illness was evident in both outbreaks. In the first, protection was roughly related to dose; in the second, all vaccinated groups appeared to be nearly equally protected. The 200-CCA-unit and 500-CCA-unit vaccines were shown to be about 68% effective in the autumn and only slightly less so in the winter. The 50-CCA-unit vaccine was about half as effective as the higher doses during the first wave but almost equally effective during the second outbreak of respiratory illness.

50 Seventh St. (23) (Dr. Dull).

Dr. Alexander D. Langmuir of the Communicable Disease Center, Atlanta, Ga., contributed to the analysis of results and preparation of the manuscript, and Dr. Roslyn Q. Robinson assisted in the completion of laboratory tests. Warden Fred T. Wilkinson of the U. S. Penitentiary at Atlanta and his assistants lent administrative support, and Drs. Kenneth Hyatt and William Wood of the Penitentiary's Medical Department collaborated in the medical administration of the program.

The vaccine used in this study was supplied by Lederle Laboratories, Division of American Cyanamid Co., Pearl River, N. Y.

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IMMUNIZATION WITH POLYVALENT INFLUENZA VACCINES

Keith E. Jensen, Ph.D., Allen F. Woodhour, Ph.D., Terre Haute, Ind.
and
Ann A. Bailey, M.D., Gracewood, Ga.

Injection of a single-strain vaccine evokes in the adult person an antibody-recall mechanism previously established by initial childhood antigenic experiences with related influenza viruses. This now bolsters antibody levels against viruses from that family of strains and provides some degree of protection against influenza caused by a new variant. To gain better understanding of age-related differences in antibody foundations in influenza immunization, groups of children and adults were given two different polyvalent influenza vaccines. The six-strain preparation (1,000 chick-cell-agglutination units) produced no greater incidence of undesirable side-effects than those obtained with the standard four-strain formula (500 CCA units) and repeatedly stimulated superior antibody responses. Children generally produced better antibody levels than did adults with use of the six-strain vaccine.

The influenza pandemic which occurred in the United States in 1957-1958 provided an excellent opportunity to determine the efficacy of monovalent vaccines. Even these hurriedly prepared prophylactics were effective, since it was shown that their use reduced clinical influenza in many different populations by as much as 77%.[1] Seroepidemiologic surveys further confirmed the premise that antibody response to influenza vaccines is a reliable index of the protection conferred by a given preparation.[2]

Although influenza infrequently results in death and is usually considered to be a mild febrile illness, severe sequelae and debilitating effects can occur. The United States Public Health Service, in the fall of 1958, recommended vaccination against influenza as the only available means of reducing the incidence of this disease. Several million cases of influenza subsequently occurred during the period January through May, 1959, in the United States, Europe, and elsewhere. These widespread epidemics lead to the usual closure of schools, and mortality due to influenza and pneumonia rose to well above normal for the season.[3] Because viruses isolated during the epidemics of 1958-1959 were shown to be closely related to the strains contained in available influenza vaccines, it is highly probable that much of this disease could have been prevented.

Successful immunization against influenza is complicated by the fact that subgroups of the two epidemiologically important antigenic types are composed of changing antigenic composites. To anticipate future antibody requirements, vaccines should include antigenic mosaics from the types A and B with sufficient breadth to combat any emergent virus variant. The simplest vaccine would be a preparation composed of two strains, one each of the most recent type A and type B isolates. A system of "watch laboratories" has been established for rapid detection of new variants, in the hope that these viruses could be quickly incorporated into vaccine. However, as was shown in 1957, a new variant may spread around the world faster than a countering vaccine can be prepared and distributed. Although our observation period is limited so that the full range of possible variation is not yet known, four sets of type A and two sets of type B viruses have now been isolated. To derive the fullest measure of immunity against the next variants that cause influenza, vaccines should incorporate a gens from each of the six known sets.

It has long been recognized that children h the highest rates of attack in all influenza epid ics. It is also a well-known fact that serum sp mens from adults contain antibodies against stra of virus which were prevalent in the many p epidemics. It is apparent, therefore, that ad derive protection from the antibody comple produced against older viruses which then cr react with the new variant. This phenomenon been examined carefully by Davenport and co-workers,[4] and they have now described in de the antibody-orienting effect of the first antige experience with influenza virus on subseque developed patterns of antibody. The concept "original antigenic sin" has provided a valua hypothesis for an understanding of age-rela variability in antibody responses to vaccination infection. Injection of a single-strain vaccine engage an antibody-recall mechanism that established as a result of the initial childh antigenic experience with related influenza viru which now has the effect of bolstering antib levels against viruses from that family of strains.

From the Biologics Research Department, Charles Pfizer and Co., Inc., and the Georgia State Training School for Mental Defectives.

a contrasting corollary, specific responses to subsequently encountered strains can be inhibited, because much of the antibody that is stimulated is lirected toward the older strain. Immunologically nature persons would appear less sensitive and nay even approach a refractile state when confronted by new antigens. To gain further insight nto the effect of these age-related differences in ntibody foundations on influenza-immunization ractices, groups of children and adults were inected with the two different polyvalent influenza accines that had been used during 1958-1959. The wo preparations differed in formula as shown in ble 1. One was adopted in 1957 for the standard ommercial vaccine, which contained a total of 500 hick cell agglutination (CCA) units per milliliter. he other formula followed the specifications recmmended by the Commission on Influenza of the rmed Forces Epidemiological Board and conained two additional strains, the A/Swine and the /Lee virus, as well as twice as much of the 2/Asian and B1/GL components as did the first.

TABLE 1.—*Composition of Two Polyvalent Vaccines Against Influenza*

Virus Strain	Chick Cell Agglutination (CCA) Units	
	500	1,000
2/Asian/57	200	400
/PR8/34	100	100
1/PR301/54	100	100
/Swine/31	...	100
1/GL/54	100	200
/Lee/40	...	100

The plan of the study was to compare antibody esponses and incidence of febrile reactions after ubcutaneous injections with various dosage schedles. The subjects were children and adults in penal nd mental institutions in Indiana and Georgia.

Methods

All subjects were bled immediately prior to vaccination, and the serums were stored until postvaccination specimens could be processed. Antibody was measured with use of a standard-pattern hemagglutination-inhibition (HI) test, and all serums were treated with trypsin and potassium periodate to destroy nonspecific inhibitors.[5] Solutions of 8 mg. per milliliter of trypsin (1:250) were prepared in M/10 phosphate buffer, pH 8.2. One volume of serum was mixed with one-half volume of trypsin and incubated for 30 minutes at 56 C. After being cooled to room temperature, the specimens were treated with freshly prepared M/90 potassium periodate in distilled water. Three volumes of periodate were mixed with serum and held for at least 15 minutes at room temperature, after which three volumes of 1% glycerol-saline were added. Serial dilutions of serum were prepared in twofold progression in dilutions of 1:10 through 1:320. When results of preliminary tests did not indicate an end-point at the highest dilution of serum, secondary titrations were conducted with dilutions through 1:2,560. The diluent for the virus, chick erythrocytes, and serum was 0.85% sodium chloride with M/100 phosphate buffer at pH 7.2. Titers are expressed as the reciprocal of that dilution of serum (before addition of other reagents) which completely inhibited four hemagglutination units of virus.

Except where noted otherwise, the hemagglutination antigens used were the vaccine strains. To measure antibody against the Asian set of variants, the antibody-sensitive line of A2/Japan/305/57 with an egg/ferret/mouse/egg transfer history was used.[6] The Asian virus used in the vaccine was the A2/Formosa/313/57, which possesses excellent antigenic potency but has low reactivity in the hemagglutination-inhibition test.

Results

Incidence of Febrile Reactions.—A frequently voiced objection to the use of influenza vaccines has been that severe reactions may occur, particularly when high concentrations of virus are used. We have studied the incidence of fever, painful injection sites, and generalized symptoms in 743 persons ranging in age from 2 to 58 years. No subjects with a history of allergy to eggs were included in this study. Only mild reactions occurred, and complaints of sore arms were no more frequent than in subjects who received a formalinized placebo. A summary of the incidence of febrile reactions is provided in table 2.

Although the number of subjects in the group of those aged 2 to 5 years was small, and conclusions regarding those observations must be guarded, the other groups were of sufficient size to provide satisfactory data. Temperatures of all subjects were recorded after 4, 12, and 24 hours, and most of the elevated temperatures were found at the 12-hour interval. In general, fever was not present as long as 24 hours, and all subjects had normal temperatures 36 hours postvaccination. With both vaccines, the highest incidence of reaction was noted in the youngest age groups, in which about 20%

TABLE 2.—*Incidence of Febrile Reactions to Polyvalent Influenza Vaccine*

		Vaccine, CCA Units					
		500			1,000		
Age Group, Yr.	Dose, Cc.	No. Vaccinated	Febrile *		No. Vaccinated	Febrile *	
			No.	%		No.	%
2-5	0.10	14	4	29	7	2	29
6-12	0.25	81	14	17	91	17	19
6-12	0.50	71	15	21	87	17	19
13-18	1.00	72	4	6	174	19	11
19-58	1.00	57	1	2	89	5	6
Totals		295	38	13	448	60	13

* Recorded temperatures 100F (37.78C) or greater at 4, 12, or 24 hours. None persisted as long as 36 hours postvaccination.

developed transient fevers. In older children and adults, frequency of fever ranged from 2 to 11%, whereas an average value of 13% holds for the entire series of 743 persons. Thus, although twice as much virus was injected with the 1,000-CCA-unit preparation, the incidence of febrile reactions was not greater than that observed with the standard 500-CCA-unit vaccine.

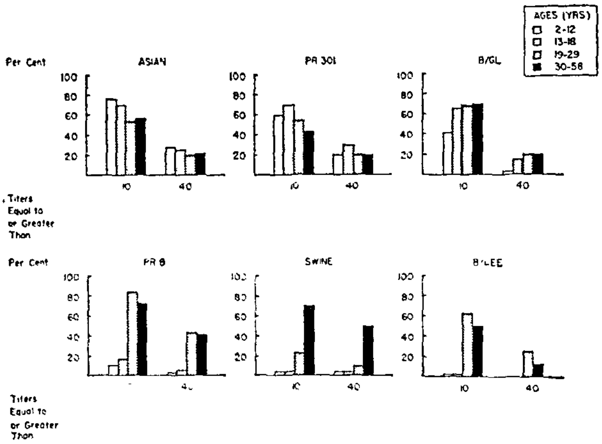


Fig. 1.—Incidence of antibody titers in prevaccination serums obtained from human subjects drawn from four age groups.

Antibody Titers in Prevaccination Serum.—Presence of antibody in prevaccination serums against the six strains of influenza and the relative frequency of various antibody titers in four different age groups are shown in figure 1. Although titers ranging from 1:10 to 1:2,560 were measured, two different levels (equal to or greater than 1:10 or equal to or greater than 1:40) have been selected to simplify presentation of the results. Over 70% of children 2 to 12 years old had antibody against the Asian variant. However, only one-third of those with antibody had titers at 1:40, the level that is usually considered protective and is generally exceeded after convalescence.[2] As expected, we found that older children had the greatest incidence of antibody against PR301, the strain that is closely related to the type A viruses that were prevalent from 1946 to 1957.

The B/GL virus was first isolated in 1954 and is practically identical to the type B strains that have been prevalent during the past seven years. It is of practical interest that the lowest incidence of antibody against the B/GL strain was found in children. That children are particularly susceptible to this variant is supported by the high incidence of type B infection that was seen in children during the early part of 1959.[3]

Age-related differences in antibody patterns are clearly illustrated in the data given at the bottom of figure 1, where it is shown that few children had antibody against older strains. Viruses similar to the PR8 have not been in circulation since 1943; variants similar to the Swine strain were epidemiologically important 40 years ago. The Lee strain was isolated almost 20 years ago and is equivalent to the contemporary type B virus. In sharp contrast to these results, adults often had antibody against the older viruses. It is known that these levels are boosted and maintained by repeated antigenic experiences with subsequently prevalent variants that are only remotely related to those strains encountered in childhood.[4] A greater percentage of subjects in the oldest age group had antibody against the Swine virus, an immunological relic of the type A-influenza strains that circulated in human beings during the decade prior to 1924.

Antibody Responses of Children to Polyvalent Influenza Vaccines.—Keeping the current prevaccination antibody titer foundations in mind, attention will be focused first on the patterns of antibody response in children (age range of 6 to 12 years) that developed after subcutaneous injections of two 0.5-ml. doses of influenza vaccine containing either 500 or 1,000 CCA units per milliliter. The second dose was given one week after the first, and blood samples were obtained two weeks after the last injection. Data from a typical experiment are illustrated in figure 2, with geometric-mean titers plotted in the upper part; geometric mean-fold increases are shown as inverted bars in the lower portion of figure 2. The six-strain preparation with 1,000 CCA units elicited superior results with every antigen. Although the vaccines contained equal amounts of the PR8 and the PR301 strains, greater responses were observed in the children who received the six-strain vaccine. It was of interest to find that the geometric mean-fold increase, when measured against the Asian strain, Japan 305, was about the same in the two groups, although the mean-antibody titer was greater for the subjects who were given the vaccine containing 400 CCA units of Asian virus. With the B/GL strain, greater re-

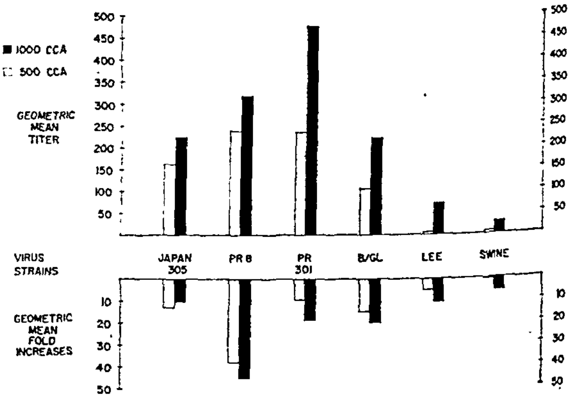


Fig. 2.—Comparison of hemagglutination-inhibiting (HI) titers and average-fold increases in serums obtained from children injected, respectively, with 500 chick cell agglutination (CCA) unit (4-strain) or 1,000-CCA-unit (6-strain) influenza vaccine.

sponses were measured either way in the children who had been given the six-strain product.

In both groups, much of the antibody stimulated against the Japan/305, the PR301, and the B/GL virus was probably of a recall nature, since most subjects had low levels against these strains before vaccination. The titers against both the Lee and Swine viruses are small in comparison with those found for other strains and can be considered as typical primary antibody responses in children who had not been exposed previously to these antigens. The titers are, in fact, quite similar to those obtained in 1957 after injections of monovalent Asian-influenza vaccines, when antibody was produced for the first time against that variant. Curiously, a few persons in the group that was given four-strain vaccine developed antibody against Lee and Swine, strains that were not present in the formula they received.

Relation of Antigen Multiplicity to Antibody Response: Is the greater antibody response to the 1,000-CCA-unit vaccine due to its larger amount of virus, or does it reflect the greater variety of related antigens that are contained in the six-strain preparation? An experiment designed to weigh these alternatives was performed by giving one group of children 1.0-ml. doses of the 500-CCA-unit product, while a comparable group received 0.5 ml. of the 1,000-CCA-unit vaccine. As in previous studies, two doses were given one week apart. By this arrangement, although total virus units were equal, the doses given to one group contained antigens of six trains while those given to the other group conained only four strains, as shown in table 3.

The distribution of antibody titers obtained in his experiment is shown in figure 3. Higher antibody levels of 1:160 or 1:640, as measured against he Asian, B/GL, and PR301 strains, occurred more often in the group that had received the six-strain ormula. The results were particularly striking with he PR301 strain. Although children who had been given six-strain vaccine were immunized with only

TABLE 3.—*Administration to Two Groups of Two Doses of Influenza Vaccine Composed of Six and Four Strains of Antigens Respectively*

Virus Strain	Groups Given CCA-Unit Vaccine (1,000 Units)	
	Six Strains	Four Strains
Asian	400	400
B/GL	200	200
PR301	100	200
PR8	100	200
B/Lee	100	...
wine	100	...
Total CCA units in 2 doses	1,000	1,000

ne-half the amount of this antigen, their responses were greater. The difference may best be accounted for by the presence of a greater variety of type A antigens in the six-strain vaccine. In contrast, when the PR8 strain was used to measure antibody, the response to the four-strain vaccine exceeded that found in the other group, since the larger amount of PR8 antigen in the four-strain formula stimulated a primary antibody response of greater magnitude.

Effect of Dosage Interval on Antibody Response: To investigate the matter of an optimal schedule for maximal response after two injections, a series of experiments were performed in groups of about 25 boys ranging from 12 to 17 years of age in which two, four, or six weeks respectively, elapsed between the first and second injections. The boys were bled prior to vaccination, at the time of the second injection, and two weeks later. As a control, one group received only one dose of vaccine and was bled after eight weeks. The distribution of the antibody titers that were obtained is given in figure 4. The length of the horizontal bar indicates percentage with titers equal to or greater than the values given on the vertical scale. The unshaded portion represents the prevaccination foundation; the lightly shaded area shows the response after one dose, and the heavily shaded portion delineates the increment found in serum specimens drawn two weeks after the second injection. Data are so arranged that the responses of all four groups can be compared with each antigen.

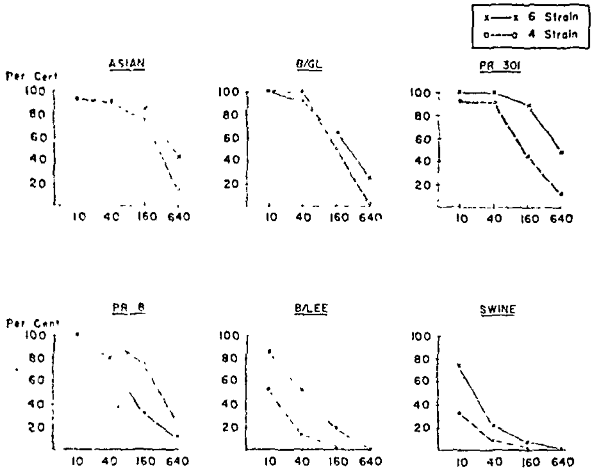
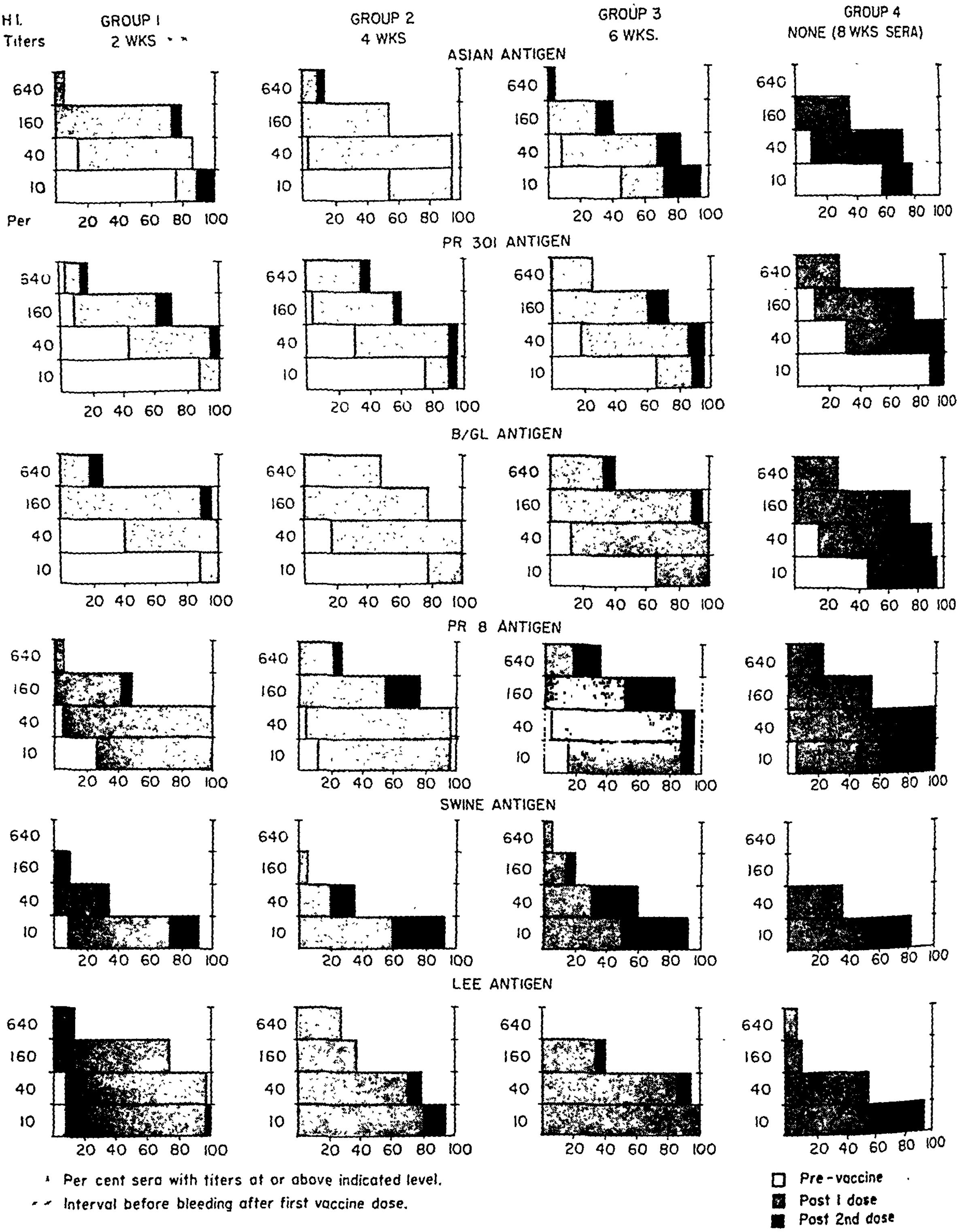


Fig. 3.—Antibody responses in children given two doses of 500 CCA units in four-strain and six-strain influenza vaccines respectively.

With the Asian virus, the maximum primary response was found two to four weeks after the first dose, and then most of the vaccinees began to lose antibody. When a second injection was given six weeks later, at least 25% responded; nevertheless, the group level was only as great as that found at four weeks after one dose, an indication that little was gained by the second injection. With the PR301 and B/GL antigens, there is little difference between the four groups. It is evident that most vaccinees had responded maximally to the first injection, probably because nearly all had been sensitized previously by experience with closely related viruses. Therefore, the antibody stimulated was due to a recall mechanism, and the subjects were refractory to a second injection at these short intervals.

In the case of the PR8 and Swine antigens, many of the children did derive benefit from a second dose. This is most evident in the responses of the subjects in group 3, in which the interval between



* Per cent sera with titers at or above indicated level.

** Interval before bleeding after first vaccine dose.

Fig. 4.—Distribution of HI antibody titers in serums obtained from children before and after one or two doses of 1,000-CCA-unit (six-strain)-influenza vaccine.

doses was six weeks. However, differences in responses of the three groups were not of sufficient magnitude to warrant a delay in giving the second dose.

Dosage Size Related to Antibody Response: In view of the superior antibody patterns obtained in children when a vaccine dose containing only 500 CCA units of the six-strain formula was injected, we investigated doses as low as 100 CCA units, with use of a 1,000-CCA-unit vaccine that was diluted 1:5 in saline solution and given as a 0.5-ml. subcutaneous injection. For comparison, a second group was given 0.5 ml. of the undiluted vaccine. Injection of these doses was repeated after two weeks, and the serum samples collected two weeks after each dose were tested with the six strains of influenza. Comparisons of the antibody response patterns are presented in fig. 5.

Although somewhat higher levels were found in he group of those who received 500 CCA units of vaccine, it is evident that a large number of chillren given only 100 CCA units developed satisfacory titers, particularly when measured against the Asian, B/GL, and PR301 strains. After receipt of he second dose, titers were, with few exceptions, ssentially like those seen after one dose of either he 100-CCA or the 500-CCA unitage. The concluion is clear that children who had received a total f 100 CCA units and, therefore, only 10 CCA units ach of the Swine, B/Lee, PR301, and PR8 strain ften responded in a satisfactory manner, and that second injection of a similar amount two weeks fter improved the group's response level only lightly.

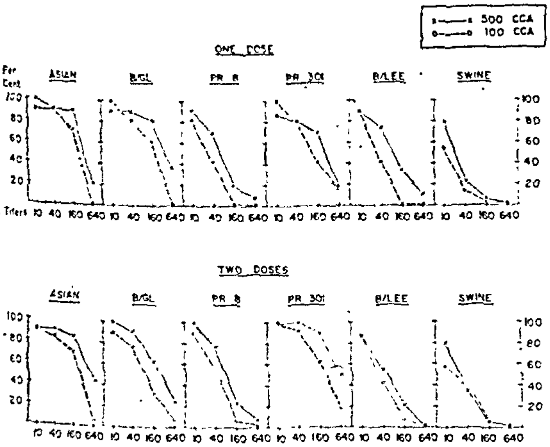


Fig. 5.—Patterns of antibody response in children injected ith 100 or 500 CCA units, respectively, of six-strain influza vaccine containing 1,000 units per milliliter.

Antibody Responses of Adults to Polyvalent Influenza Vaccine: The pattern in adults varied considerably from that found in children. Although, as shown in figure 1, the incidence of prevaccination antibody to all strains was greater in adults, children responded to vaccination more frequently. This effect did not parallel increasing age, except in measurements against the oldest available virus, i. e., the Swine strain. Therefore, to simplify presentation, the data are grouped from all persons who were aged 19 years or older; the median age was 27 years.

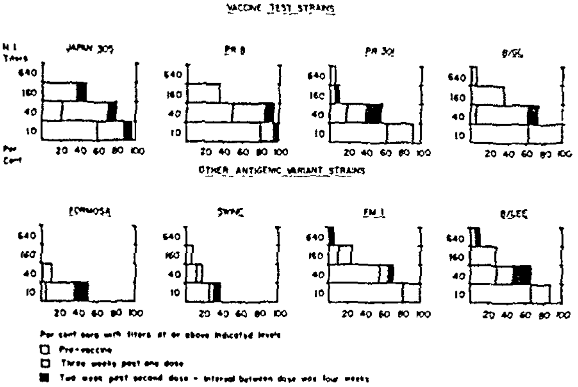


Fig. 6.—Distribution of HI antibody titers in serums obtained from adults before and after vaccination with standard four-strain polyvalent influenza vaccine.

To study the increment that might be gained by giving a second dose of vaccine at a relatively short interval after the first, injections of 1 ml. of four-strain, 500-CCA-unit vaccine were given subcutaneously to 26 adults. They were bled three weeks after the first dose and two weeks after the second, with a four-week interval between injections. The distribution of antibody titers is shown in figure 6, with responses to the strains used in the vaccine illustrated in the upper part and as measured with other different strains in the lower portion of the chart. As was true for children, relatively few adults reacted to the second dose. The best responses were obtained with the Japan 305 and B/GL strains that are representative of the currently epidemic type A and B variants. It is remarkable to find that, although most adults have low levels of antibody against many of the older strains, and can therefore be considered sensitized, vaccination did not elicit hyperimmune responses. It is evident that in many adults antibody titers reach a ceiling or normal maximum, subsequent to which, in a sense, these persons become desensitized after multiple antigenic experiences during the recurrent progression of influenza epidemics.

Results of several experiments with the two polyvalent influenza vaccines in adults indicated that the 1,000-CCA-unit preparation stimulated better antibody responses more often, although the degree of superiority was not as great as that seen in children. The results of two such experiments are illustrated in figure 7. In this case, the effectiveness of vaccination is compared on the basis of the percentage of each group without significant antibody titers before and after vaccination. By this means, attention is focused on that portion of the population which appears to be in greatest need of an effective vaccine.

Prior to immunization, about 50% of each group studied had serum titers of less than 1:10 against the Swine strain, and 65% of the titers were less than 1:40. In the group that had received the 500-CCA-unit vaccine only a few developed antibody, while, in contrast, 80% had detectable levels after vaccination with the 1,000-CCA-unit preparation. This response to the Swine strain is not entirely satisfactory, however, since only 55% produced titers equal to or higher than 1:40. The Lee, GL, and PR8 viruses elicited better group responses. It was only with four strains, namely, Lee, GL, PR8, and Swine, that the group that had been given the 1,000-CCA-unit vaccine showed any degree of superior response, whereas measurements with the PR301 and Japan 305 viruses indicated no difference between the two vaccines. The PR301 strain must be considered a particularly poor antigen in adults, since about 10% of each group remained without antibody levels equal to 1:10 and 50% did not have titers equal to 1:40 after vaccination.

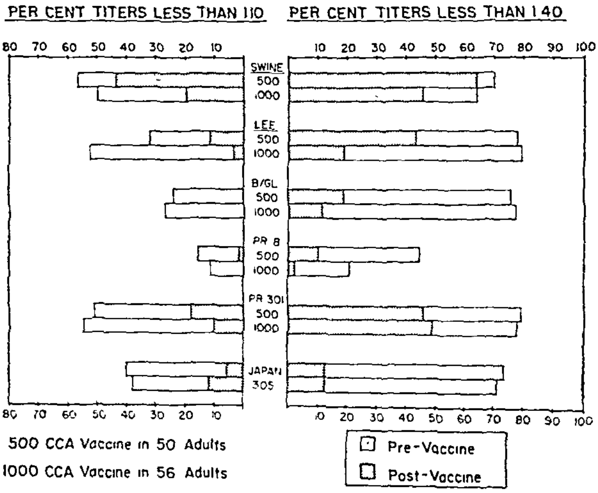


Fig. 7.—Evaluation of polyvalent vaccines by efficiency of conversion of low antibody titer level in adult populations.

About 10% of the adults failed to produce antibody to the Asian component to a level of 1:40 or higher. This was the case regardless of whether 200 CCA units, as provided in the 500-CCA-unit polyvalent vaccine, or 400 CCA units of this component were given.

When one compares the antibody patterns obtained in adults and children with the two different polyvalent vaccines, it is evident that children, in general, responded to influenza antigens in a satisfactory manner more often than did adults (fig. 8). Furthermore, the superiority of the six-strain preparation is most evident in children.

Comment

Since 1947, when the antigenic change amor type A strains to the A1 set was shown to be practical immunological significance, there h been uncertainty as to what degree of differen among antigenic variants is necessary to warra their inclusion in a polyvalent vaccine. The pra tice has been to revise almost yearly the formulati of influenza vaccines. Many serologic variatio among the virus isolates were found to represe "antigenic embroidery" of little significance wi regard to the protection of human population Although influenza viruses have appeared capal of random variations in antigenic structure sin the first isolations three decades ago, it is now p sible to group these variants into families or sel Herein lies the key to successful immunizati since vaccination with one representative of a induces antibody formation and protection agai other members of that group. A new family becon prevalent and completely replaces its ancest group of strains with almost predictable regulari Since new sets of both type A and B viruses can expected to appear in a few years, how can we b prepare for them? What are the mechanisms whi produce the marked shifts in antigenic structu There are as yet no completely acceptable and g erally satisfying answers to either question. optimistic but rational hypothesis is that suffici antigens may be shared by members of the differ sets to provide immunological overlapping in p sons of wide experience with influenza varian who would, therefore, be insensitive to infectio with ensuing generations of influenza strains. Th is supported by the observations that highest rat of attack in influenza epidemics occur among chi dren. This is the basis for compounding a vaccir

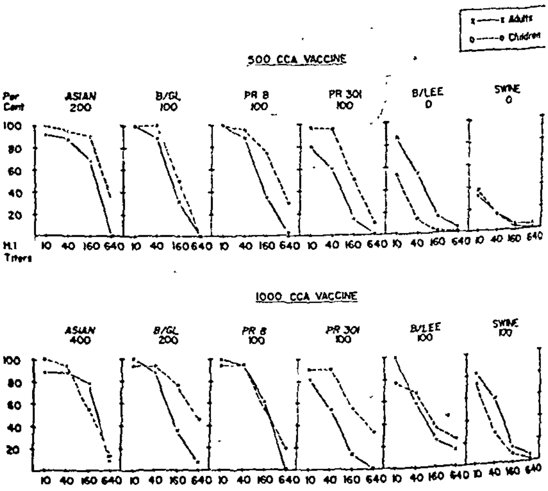


Fig. 8.—Patterns of HI antibody titer distributions serums obtained from children and adults after vaccinati with four-strain and six-strain influenza vaccine respective

that contains representatives from each of the sets of virus known to have been successively prevalent during the past 30 years.

The antibody responses of children and adults to monovalent (single-strain) influenza vaccines have been well characterized in reports on the recent widespread experience with the Asian strain [1] and in such previous studies as those of Davenport and co-workers.[4] The concept that the antibody orientation is the result of the initial influenzal antigenic stimulus in life has provided a valuable hypothesis for understanding the age-related variability in antibody responses to vaccination or infection. Responses to influenzal antigens are governed by antibody-recall mechanisms established as a result of the first antigenic experiences in childhood with related influenza viruses. The most obvious effect is a bolstering of antibody levels measured against viruses from that family of strains. On the other hand, responses to subsequently encountered strains may in some cases be inhibited; indeed, it can be expected that well-seasoned persons will become relatively refractile in producing antibody against the most recently experienced antigens. These aspects of influenza immunization, first observed after injections with monovalent vaccines, clearly affect the results that will be obtained when multivalent preparations are given. However, persons of any age can be immunized to a great variety of influenza variants by the simultaneous injection of several strains.

That the continued use of polyvalent influenza vaccines should be encouraged is supported by recent epidemiologic observations [3] and by our serologic findings that most children, in particular, have little, if any, antibody against the important influenza strains. Our data make it evident that antibody production stimulated by vaccination or natural experience even in the recent past has not been maintained at desirable levels in most subjects. It must be concluded that the greater portion of previously infected persons may be susceptible to reinfection and, therefore, antibody titers should be boosted by additional antigenic experience through vaccination. It is now clear that children can be provided with antibody complexes comparable to those found in older adults by immunization with a six-strain vaccine.

The question of the proper formula for the most successful influenza vaccine has been approached in these studies by a comparison of antibody responses to the vaccines that are now available. Since it is not possible to make an accurate prediction, we must continue the attempt to second-guess the antigenic composition of the next sets of influenza viruses which are likely to appear in the near future. At this point in time, the best recourse is to manufacture polyvalent influenza vaccines that contain a spectrum of efficacy that is provided by the most antigenic representatives of each of the past families of variants. The data obtained from our study indicate that vaccines containing six strains are efficacious and, further, that a new formula for a vaccine which includes from 10 to 100 CCA units each of these strains would be as safe but more potent than the current four-strain 500-CCA-unit standard vaccine. Its use would cause, particularly in children, formation of immunological barriers of greater breadth against new influenza-virus varients.

Summary

Two polyvalent influenza vaccines were given to both children and adults and compared for their safety and potency. Injection of a six-strain preparation, with a total chick cell-agglutination unitage of 1,000, while producing no greater incidence of undesirable side-effects than lower doses repeatedly stimulated antibody responses that were superior to those obtained with the standard four-strain formula of 500 CCA units. Children generally produced better antibody levels than adults with use of the six-strain vaccine. Secondary injections are usually needed to maintain the antibody level and should not be delayed unduly. Use of the six-strain vaccine in the unitage indicated above should provide broader immunological barriers against new influenza-virus variants.

The vaccines used in this study were supplied by the biologics production department of Charles Pfizer & Co., Inc., Terre Haute, Ind.

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PNEUMATOSIS CYSTOIDES INTESTINALIS

Howard P. Doub, M.D.
and
James J. Shea, M.D., Detroit

The authors give the histories of four patients with collections of air under the mucosa or serosa of the intestinal tract and its peritoneal attachment. The 4 are representative of 16 patients, observed by the authors, with pneumatosis cystoides intestinalis and a common history of allergic difficulties and asthma. The etiology of the disease has been the subject of many theories, but a complete understanding of the pathogenesis has not yet been attained. The two dominant concepts at present are based on (1) a mechanical theory which assumes that the gas is forced through a fissure in the intestinal mucous membrane and (2) a chemical theory which assumes that gas is produced by fermentation and absorbed by the mucous membrane. Investigation for the existence of a cause-and-effect relationship between allergy or asthma and air in the intestinal wall is suggested as a worthy endeavor.

Pneumatosis cystoides intestinalis is an uncommon disease characterized by submucosal or subserosal collections of air in the intestinal tract and the peritoneal attachments. Pneumatosis coli is the more specific term for its localization in the colon, which is the subject of this report. Koss[1] in 1952 reviewed the world literature and found a total of 255 cases, but only 13 of these were limited to the colon. To the latter group, some 18 cases in adults have since been added.[2] This report is based on a study of 16 cases.

Symptoms and Etiology

Symptoms occur in most patients, but these are nonspecific, being common to any number of conditions involving the colon or small intestine. Bouts of diarrhea alternating with constipation, constipation alone, melena, and flatulence are common. Any of these may occur as an isolated finding, or they may be present in combination. A few cases are asymptomatic initially. In one patient in the present series roentgenograms showed evidence of the disease more than two years before he complained of any symptoms referable to the colon. The onset of symptoms frequently prompts radiologic studies and proctoscopy, leading to recognition of the disease.

Two forms of pneumatosis coli are recognized, the primary, which does not involve the rest of the gastrointestinal tract, and the secondary, in which there is an associated obstructive lesion in the stomach or small intestine. In the latter instance, it is the small intestine which is mainly affected. Koss[1] found that 58% of the patients whose cases he studied had stenotic lesions in the pyloric area, most of which were ulcers.

The mechanical theory of the disease postulates a break in the mucosa through which air is forced under pressure into the submucosa or subserosa, probably by way of the lymphatic channels. It does not, however, explain the separated areas of involvement encountered in the small intestine and certainly does not account for the fact that the

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From the Department of Radiology, Henry Ford Hospital.

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disease is situated solely in the colon. Stienon[3] explained multiple areas of involvement by suggesting that the gas extends retroperitoneally and, having reached the mesenteric insertion of the intestine, either enters the subserosal spaces or follows the perforating blood vessels into the submucosal space. Marshak[2a] has considered the traumatic role of sigmoidoscopy and biopsy in the production of pneumatosis in the left half of the colon. Alford[2d] proposes a chemical theory, attributing the symptoms of diarrhea, flatulence, and abdominal distress to increased fermentation in the large intestine, with an increase in lactic acid and gas-forming bacteria. He postulates an alteration in the normal absorption of gases by the blood stream with retention in the wall of the intestine. The gas bubbles then may lead to the formation of giant cells and connective tissue which encapsulates the gas to produce cysts. There are many theories about this disease, but there is no established cause.

Pathology

Koss[1] outlines the possible sequence of events as follows. The simple endothelial cells with which the cysts are lined have a tendency to coalesce to form large giant cells. An associated inflammatory reaction occurs in the adjacent connective tissue. The giant cells finally slough, the surrounding stroma and the cysts become fibrotic, and the cysts disappear as scarring progresses. The cysts vary from a few millimeters to a few centimeters in diameter. They may occur either singly or in clusters. They apparently do not communicate with the intestinal lumen or with each other. In the colon they are located predominantly in the serosa, but they may be submucosal.

Roentgenographic Studies

The diagnosis of pneumatosis coli can be made from the chest film, in which air cysts (fig. 1) may be seen in the splenic or hepatic flexure of the colon, or from a plain film of the abdomen. Either may be confirmed by barium enema. With involvement of the splenic or hepatic flexure the cysts can be seen as small gas shadows adjacent to or superimposed on the air in the colon (fig. 2). In one of the cases in the present series the diagnosis was suggested by a photofluorogram. Barium enema study demonstrates large polypoid defects in the wall of the intestine. Sometimes the barium practically obliterates the cysts, and they are not well visualized except on the postevacuation film, in which the collections of air are seen at the periphery of the intestine because of the contrast between them and the barium-coated mucosa. At times in the postevacuation film the mucosa appears to be swollen, which suggests ulcerative colitis. Close inspection, however, discloses the air cysts at the margin of the intestine (fig. 3). The gas may also be evident as a linear radiolucent stripe along the intestinal margin.

Roentgenographic evidence of pneumoperitoneum in an asymptomatic patient should suggest pneumatosis intestinalis. A correct roentgenographic diagnosis will prevent unnecessary surgery. No patient in this series was operated on, and there were no complications, though such complications as obstruction from pressure of the cysts, volvulus as a result of the scarring, and pneumoperitoneum have been recorded by others. In one case retroperitoneal air was present beneath the diaphragm bilaterally.[4] It showed no shift regardless of the position in which the films were taken and produced no specific symptoms.

Report of Cases

Case 1.—A 64-year-old man was first seen in August, 1953, because of bronchial asthma. It was fairly well controlled, but exacerbations occurred from time to time, usually precipitated by acute upper respiratory infections. The patient was not seen from April, 1954, until July, 1955. At the latter time a barium enema examination demonstrated pneumatosis cystoides in the sigmoid area and distal portion of the transverse colon. A proctoscopic examination on the preceding day had shown no significant findings. A second barium enema study in August, 1956, showed regression of the previous areas of pneumatosis cystoides in the sigmoid and splenic flexure. The patient died January, 1958, because of an acute attack of asthma followed by congestive failure and ventricular tachycardia. No autopsy was performed.

Case 2.—A 49-year-old man was first seen in 1949 because of asthma which had begun four years earlier. There were repeated visits and admissions to the hospital because of exacerbation of the asthma and superimposed pulmonary infections. In March, 1955, the patient was seen because of his asthma but complained, in addition, of intermittent diarrhea. Chest films at this time showed fibrotic changes in both lungs. There was also noted an unusual collection of gas in the colon beneath the left leaf of the diaphragm.

In May, 1955, the patient reported that he had had diarrhea for five weeks, with five or six stools per day. The stools were watery and contained mucus and occasional blood streaks. Physical examination disclosed an irregular movable mass in the left upper quadrant which did not move with respiration. A barium enema study showed numerous polypoid-like defects involving the splenic flexure and the entire descending colon. Proctoscopy through a distance of 10 in. showed numerous sessile gelatinous-appearing polyps of varied size. An upper gastrointestinal examination showed negative results. The proctoscopic examination was made before the barium enema was given but six weeks after the unusual collection of gas was noted on the chest film. A barium enema given seven months later to check progress showed pneumatosis from the distal transverse colon to the middle of the descending colon. The patient still complained of three or four loose bowel movements per day, two or three times a week.

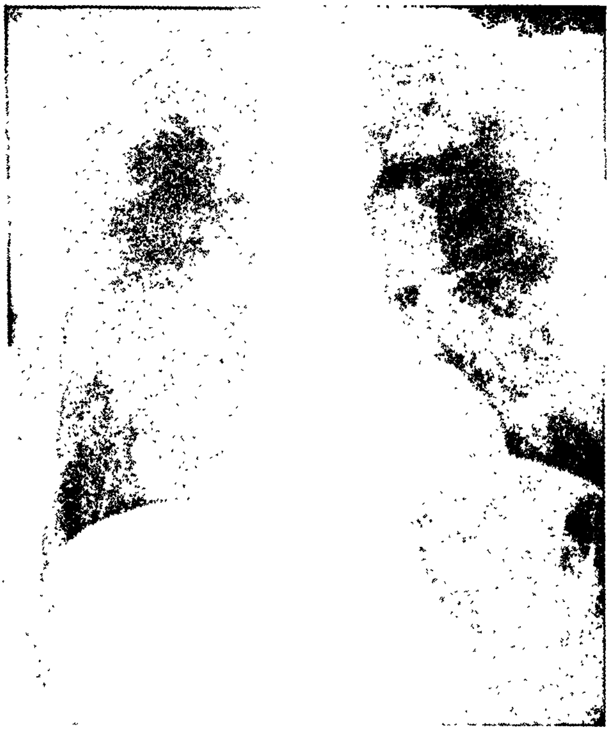

Fig. 1.—Foamy appearance of air in splenic flexure indicating air cysts.

Case 3.—A 67-year-old man had a 20-year history of productive cough with increasing dyspnea. This chronic lung condition was complicated by several acute respiratory infections each year with production of profuse mucopurulent sputum. Pulmonary function studies showed a diffuse airway obstruction, probably with some pulmonary fibrosis, and vital capacity was estimated at 50% of normal.

One and one-half years after his initial visit, the patient returned to the hospital because of blood in the stool and a large amount of flatus. A barium enema examination showed an ulcerative process in the left half of the colon and air cysts. An upper gastrointestinal series showed negative results. On subsequent visits the patient reported no further bowel difficulty. He was admitted six months after the first admission because of sudden onset of epigastric pain with nausea and vomiting. Films of the abdomen at that time showed pneumatosis cystoides in the distal transverse and descending colon. Proctoscopy prior to the earlier barium enema studies had revealed no abnormalities. The symptoms on the last admission were attributed to cholecystitis, and a cholecystogram showed cholesterol stones.

Case 4.—A 62-year-old man was admitted in January, 1953, because of acute pancreatitis. He was next seen in April, 1956, when his chief complaint was shortness of breath. Dyspnea had been present for many years but had become progressively worse, especially since an attack of severe substernal pain a week prior to his admission. An electrocardiogram showed evidence of a recent myocardial infarct. The diagnoses of arteriosclerotic heart disease with atrial fibrillation and chronic bronchitis were made.

The first suggestion of gastrointestinal involvement occurred in December, 1957, at which time he complained of having to evacuate immediately after each meal. In the interim he had had repeated attacks of asthma with superimposed respiratory infections. He was again seen five months later because of diarrhea after meals. He experienced no nausea or vomiting, and no blood was noted in the stools. He returned in June, 1958, still complaining of diarrhea, which was not responding to dietary measures or antispasmodics. At that time an annular irregular mass was felt within 2 in. of the anus, and sigmoidoscopy disclosed a mass involving the entire circumference of the intestine starting at a distance of about 6 cm. and extending

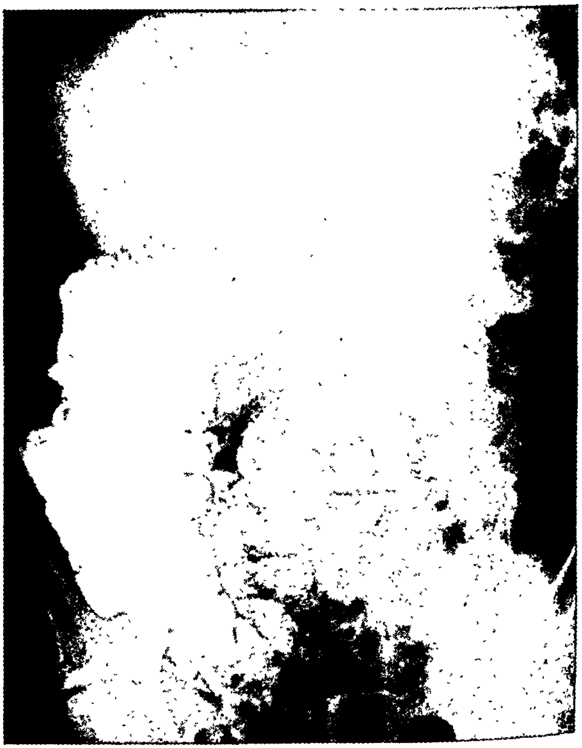

Fig. 2.—Small intestine series. Unusual small rounded air shadows in splenic flexure and descending colon are air-containing cysts.

beyond the limit of the sigmoidoscope. The surface was smooth and soft and looked like blebs. Biopsy specimens were taken of four separate areas, and "each bleb, when biopsied, yielded a report as of a balloon popping, clearly audible through the room." The surgeon's impression was pneumatosis coli involving the sigmoid and rectum. Pathological study showed normal rectal mucosa. A barium enema study a week later confirmed the findings, shown by proctoscopic examination, that there were pneumatosis cystoides involving the sigmoid colon. A study of the small intestine showed negative results.

The patient was readmitted in October, 1958, with pneumococcic pneumonia involving the left lower lobe. There was no complaint of any gastrointestinal trouble at that time.

Comment

The significant feature in 15 of the cases was a history of asthma and allergy. These patients originally and primarily sought advice about these conditions. The other patient had idiopathic pulmonary fibrosis with marked reduction of all categories of pulmonary function. It was only later in the course of the chronic lung disease that symptoms of diarrhea, flatulence, constipation, and blood or mucus in the stools developed. This association is not considered coincidental. Creevey's patient had allergic manifestations including hay fever, asthma, arthralgias, and eczema for 20 years.[2c] Matthew's patient had also been a chronic sufferer from asthma.[2f] In other reports reviewed this association had not been noted.

The exact relationship between the asthmatic and allergic conditions and the pneumatosis is not understood. The cases in this study are all confined to the descending colon except for one case involving the ascending colon. Proctoscopy, usually performed before a barium enema examination, might possibly be a precipitating factor, but in five instances cysts were seen prior to the barium enema, and several cases were diagnosed by proctoscopy initially and confirmed by barium enema. Other cases were detected by chest films prior to proctoscopy. Thus there does not seem to be a constant etiological relationship between proctoscopy and the development of pneumatosis. In none of these cases was there a history or clinical or roentgenographic evidence of obstructive disease of the stomach or small intestine. Symptoms are probably due to the cysts but their occurrence does not necessarily presuppose a complication such as partial obstruction. Symptoms may wax or wane without significant change in the degree of involvement, and pneumatosis may occur without symptoms, though these often develop subsequently. The cysts may regress spontaneously.

Differential diagnosis is not difficult. After recognition of the disease conservative treatment is indicated except in the unusual case of obstruction due to the cysts, volvulus, or uncontrollable hemorrhage.

Summary

A description of 16 cases of pneumatosis cystoides intestinalis involving the colon has been added to the previous reports of this disease. Many of these cases can be recognized or suspected from plain films of the abdomen or chest and then confirmed by means of barium enema. The diagnosis may occasionally be made by proctoscopic examination.

No cause of this lesion has ever been proved, although many theories have been advanced. It is of interest that in 15 of the 16 cases it was allergy and asthma which led the patient to seek medical care. While it is impossible at this time to establish a definite causal relationship between these conditions and pneumatosis coli, it is believed that further study should be made with this possibility in mind.

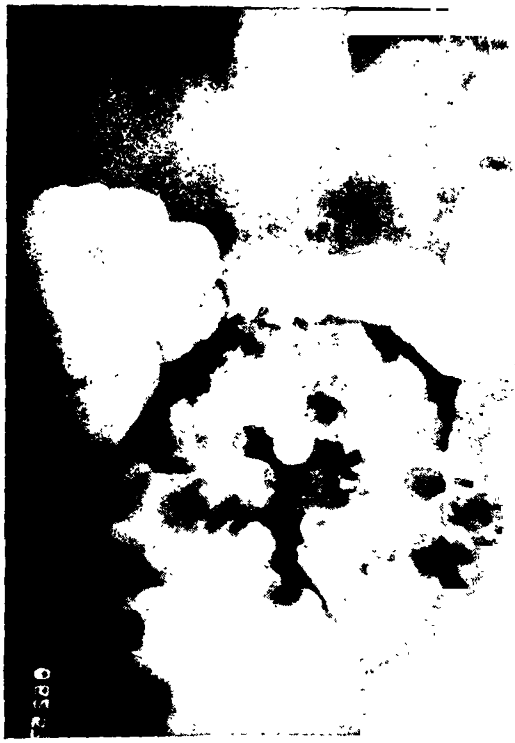

Fig. 3.—Large polypoid defects resembling polyposis. Air density at margin of intestine is well seen in splenic flexure. Pneumatosis cystoides intestinalis is proved by biopsy.

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TREATMENT OF CALCANEONAVICULAR BAR

James I. Kendrick, M.D., Cleveland

A calcaneonavicular bar, when complete, seems to join the whole of the lateral aspect of the os naviculare to the calcaneus; it replaces the calcaneonavicular ligament, produces rigid fusion of the corresponding joint, and generally causes pain. Another anomaly, a talocalcaneal bridge, is commonly associated with it. In a series of two girls and five boys with feet made painful by these anomalies, there were four feet with complete and seven feet with incomplete bars. In the younger patients in whom the bar was incomplete, simple resection was successful and good motion returned to the subtalar joint. When the bar was complete, neither conservative measures nor simple resection relieved the pain, so that triple arthrodesis was necessary.

A calcaneonavicular bar is a congenital anomaly consisting of bony bridging between the calcaneus and the navicular bone. This unusual bone formation replaces the calcaneonavicular ligament, producing a rigid fusion, which causes foot strain d associated symptoms.

Reports on the treatment of peroneal spastic flatot due to calcaneonavicular bar in children have een few, and I should like to bring this subject to your attention and to discuss it in the light of my experience in treating a number of such patients during the past 10 years.

Jack,[1] in 1954, pointed out that the papers of Slomann,[2] in 1921, and of Badgley,[3] in 1927, have been neglected, and that the important role of the calcaneonavicular bar and the talocalcaneal bridge in peroneal spastic flatfoot received attention and much-needed emphasis from the report of Harris and Beath[4] in 1948. Anatomists had described these anomalies, but the correlation of anatomic with clinical findings was due to better roentgenographic techniques and the exact visualization of the nature of these structural variations.

On the basis of my experience and the reports of others, it should be emphasized that any child who has a painful foot with peroneal spasm should undergo proper roentgenographic examination to confirm the presence or the absence of one of these anomalies as the cause of the complaint. It should also be pointed out that, since the anomalies coexist more often than not, the roentgenographic study should include the special oblique-lateral and superoinferior views of the os calcis so that exact evaluation can be made.

Nature of Anomaly

Incidence.—The condition is more frequent in boys than in girls. In the group reported here there were five boys and two girls. Three boys and one girl each had both feet involved. Two of the boys had both talocalcaneal bridge and calcaneonavicular bars bilaterally. The girl who had both feet involved had the combination bridge and bar in

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From the Department of Orthopedic Surgery, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute.

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one foot and only a calcaneonavicular bar in the other. The ages of the patients at onset of symptoms ranged between 9 and 12 years; the earliest age was in a girl. Trauma was an uncommon cause of the onset of the symptoms, which developed insidiously and seemed to be associated with the process of skeletal maturation.

Symptoms.—Pain was the most common complaint. Of the 11 feet, all but 2 were painful. Restriction of motion was the most common finding. Eight feet showed peroneal spasm; one foot showed anterior tibial spasm, and the two painless feet showed no restriction of motion. Local tenderness over the region of the calcaneonavicular bar was a frequent finding but was not present when there was a complete bar. The tenderness was just distal to and below the sinus tarsi. All patients experienced fatigability and aggravation of the symptoms by activity. None had obtained relief by either arch supports or rest. None had had manipulations performed or been given walking casts.

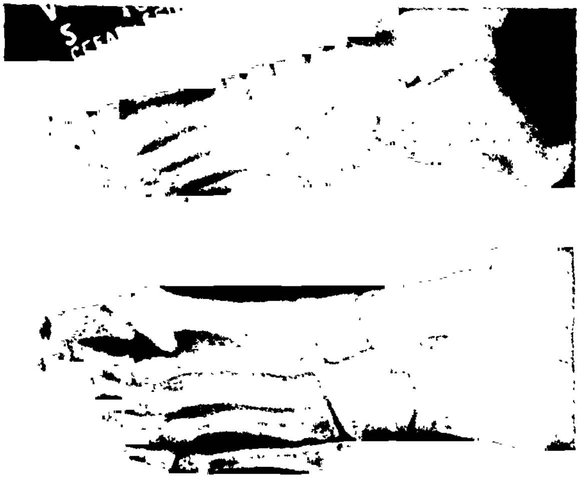

Fig. 1.—Roentgenogram showing bony bridge between calcaneus and navicular bone.

Roentgenographic Findings.—Complete diagnostic roentgenographic examinations were made of all 11 feet. The appearances of the calcaneonavicular bars varied widely. In 4 of 10 feet the bar was broad, complete, and bony throughout (fig. 1). The complete bars seemed to join the whole of the lateral aspect of the navicular bone and to flow to the inferior surface to form an extensive attachment. The other seven feet contained bars of variable structure, but all showed a radiolucent interval of either cartilage or fibrous tissue.

Pathology.—It is my belief that in early life the calcaneonavicular bar exists as a cartilage or a fibrous mass. This tissue is flexible, and its structure is adapted to movements with the joints of the midfoot. As age advances, the character of the tissue changes, and the bar becomes evident. One of the boys in this series, whose symptoms developed insidiously at the age of 11 years, had injured his foot two years earlier. A routine roentgenogram was made at that time, and I was able to review the film without finding in it any evidence of the bar that subsequently developed. The injury had been treated as a sprain, and the foot had recovered and remained painless for two years, until the onset of the peroneal spasm. This bar was removed en bloc from the youngest patient, a girl who had combination bars in both feet but pain in only one foot; she also had anterior tibial spasm. In the gross specimen (fig. 2), bone, cartilage, and fibrous tissue are recognizable, and the appearance is that of a synchondrosis. The microscopic section (fig. 3) shows bone, cartilage, and fibrous tissue on both sides and a space lined with

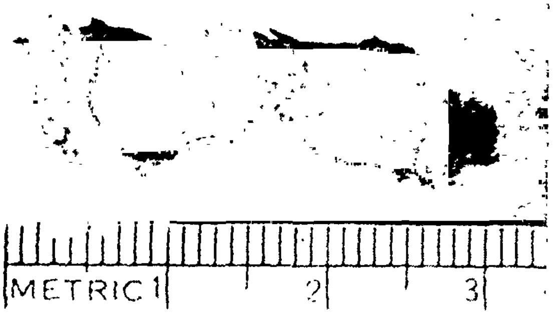

Fig. 2.—Gross appearance of resected specimen of incomplete bar, showing bone, cartilage, and fibrous tissue.

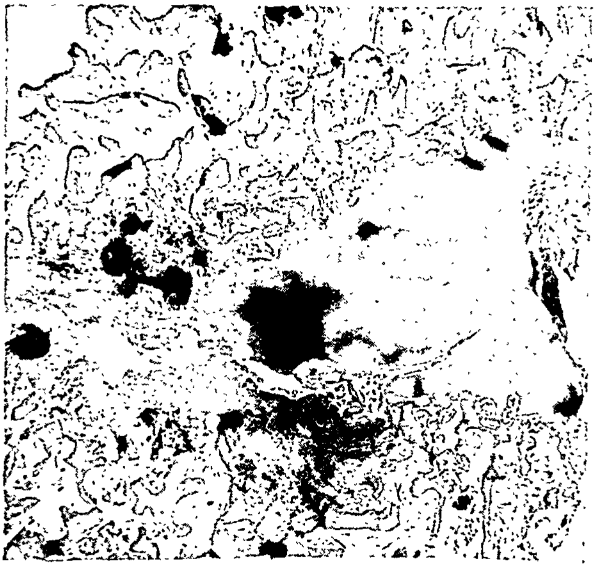

Fig. 3.—Photomicrograph of incomplete bar, showing bone, cartilage and fibrous tissue (× 12).

cells that are similar in appearance to synovial cells. This morphologic appearance is similar to that of the specimen shown by Webster and Roberts[5] in their report in 1951. The tissue noted in their case seemed more mature, and there was no evidence of a space that simulated a joint space like that seen in this case.

Treatment

In describing the treatment, I shall present the material as an analysis of the treatment of the 11 feet rather than of the seven patients. In the four feet with the broad complete bars, two of the bars were resected, and fat was interposed in the defect. Neither patient obtained relief from the operation, and one bar had re-formed completely within one year after the operation. Among these four feet, relief of symptoms was achieved in three by triple arthrodesis, but one foot remained painful and unimproved by resection of the bar. Of the seven remaining feet in which the calcaneonavicular bars were incomplete, two were painless and required no treatment. One bar was in the foot of a child who had had poliomyelitis, and the symptoms were controlled by a brace that was worn of necessity. Of the four remaining feet, all obtained prompt and complete relief of symptoms by resection of the bar, and all had subsequent return of good motion to the subastragalar joint.

Comment

Calcaneonavicular bar is not a common condition. I have examined hundreds of children's feet to gather together the seven cases presented here.

Although the number is small, I believe that the analysis of the results obtained from treatment, gives some indication of the results to be expected and which type of patient will respond to simple resection with effective relief of symptoms. In the younger patients in whom the bar was incomplete, simple resection was successful and good motion returned to the subastragalar joint. In the patients in whom the bar was complete, the pathological changes apparently were more extensive, and simple resection was not successful in either relieving the symptoms or effecting improvement in subastragalar motion. In these patients, triple arthrodesis was necessary to relieve the pain.

Summary and Conclusions

Calcaneonavicular bar is a rare condition, but nevertheless it should be considered when a preadolescent or early adolescent child has pain in the foot or feet, with evidence of either peroneal or anterior tibial muscle spasm.

If a bar exists and symptoms are well established, conservative treatment seems to be ineffective in giving lasting relief of pain. It is best to identify the bar early and to recognize that symptoms can develop in preadolescence; in those patients in whom the bar is incomplete, it can be successfully resected.

In patients in whom the bar is complete, the pathological changes are more extensive, and simple resection of the bar may not result in relief of pain.

2020 E. 93rd St. (6).

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LEPROSY IN JAPAN.—There are 15,000 leprosy patients in Japan, as contrasted with 30,000 in 1904. I visited the National Leprosorium, Zama Zensho-En, near Tokyo, a 50-year-old institution which has been gradually enlarged but hardly modernized. At present it has a capacity for 1,570 patients. It spreads over 97 acres and the patients are living in 257 houses, all surrounded with pretty gardens. The houses are extremely simple but scrupulously clean wooden structures. In addition, there are hospital buildings for the acutely ill. Strangely enough, in some wards the sexes are not separated. There are facilities for agricultural work, all kinds of handicraft, and sport facilities. Among the 32 full-time resident physicians, all specialties are represented. The medical care is at highest modern standards. The plastic surgeon, who happened to be my guide through the premises, showed me marvels in reconstruction of mutilated ears, noses, hands, and feet. Seventy per cent of the patients had lepromatous leprosy, but only 20% were active. The preferred sulfone preparation is glucosulfone (Promin); sulfoxone (Diasone) is thought to be less effective.—S. Rothman, M.D., A Dermatologist's Trip to Japan, *A. M. A. Archives of Dermatology,* July, 1959.

CONGENITAL DISLOCATION OF THE HIP

STUDIES IN THE EARLY WALKING GROUP

Edward A. Nalebuff, M.D.
and
Paul L. Norton, M.D., Boston

The authors analyze their experience with 31 cases of congenitally dislocated hip occurring in 21 patients. In all cases treatment began with closed reduction between the ages of 1 and 3 years. Twenty-two hips were immobilized in the so-called frog leg position and nine in the position of abduction and internal rotation. The frog leg position was effective only in 8 cases; the other 14 hips were changed to abduction with internal rotation, and 7 of these changes were accompanied by open reduction. Six case histories illustrate the occasional success of the frog leg position, the advantages of abduction and internal rotation, and the plan of treatment now recommended by the authors. This consists of an initial closed reduction followed by immobilization in abduction-internal rotation, combined with rotation osteotomy in selected cases.

In spite of an increased awareness of congenital dislocation of the hip by the medical profession, patients with this crippling condition are still being discovered late and are starting treatment long after they start to walk. This paper is a review of our experience with this group at the Lakeville State Sanatorium during the period 1949 through 1958. It was undertaken in order to develop an improved and more logical method of management of future cases.

This report is limited to our experience with an early walking group, between the ages of 1 and 3 years. The greatest variety of opinions exists about treatment of this particular group. Problems such as closed reduction versus open reduction; immobilization in the "frog leg" position versus abduction and internal rotation; the importance of anteversion and its management by rotation osteotomy; and the place of shelf stabilization procedures are all controversial. By excluding cases of congenital dislocation of the hip associated with other skeletal deformities such as spina bifida, arthrogryposis, and cerebral palsy, which alter both the prognosis and the treatment, we were able to study 21 patients, with a total involvement of 31 hips. All of these patients began treatment between the ages of 1 and 3 years.

Material and Methods

Description of Group.—There were 17 girls and 4 boys in the group investigated. The average age at time of diagnosis was 17 months. The average age at admission of patients initially treated at Lakeville was 21 months. Patients admitted to Lakeville for final treatment averaged 26 months of age. There were 11 patients with unilateral involvement and 10 patients with bilateral dislocations, making a total of 31 hips available for study.

Treatment.—Every hip had an initial closed reduction. Figure 1 illustrates the position of immobilization used. Twenty-two hips were immobilized in the so-called frog leg position. Nine hips were immobilized in abduction and internal rotation and required no alteration in position. However, only 8 of the 22 hips treated in the frog-leg position were successfully stabilized. The remaining 14 hips required an alteration in treatment to achieve stability. The position of immobilization was changed to abduction with internal rotation for this entire group, half of them associated with open reduction. This alteration in treatment was usually initiated because of failure of prolonged immobilization in the frog leg position to achieve stability. In two hips initially reduced in the frog leg position the position of immobilization was changed intentionally, after a short period, as part of their planned treatment. In the patients whose hips had redislocations, x-ray examination showed excessive anteversion as measured by the true lateral view, and several of these patients underwent rotation osteotomies in association with the change of position of immobilization. Excessive anteversion was visualized in each hip which underwent open reduction and in five of these hips the redislocation was anterior. Several shelf procedures were performed and rotation osteotomy for anteversion was often carried out.

Resident in Orthopedic Surgery, Veterans Administration Hospital in affiliation with Lakeville State Sanatorium, Middleboro, Mass. (Dr. Nalebuff), and Chief of Orthopedic Surgery, Lakeville State Sanatorium, and Visiting Orthopedic Surgeon, Massachusetts General Hospital (Dr. Norton). Dr. Nalebuff is now a National Foundation Fellow in Orthopedic Surgery.

Read before the Section on Orthopedic Surgery at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

It should be noted that in no patient whose hip was either initially immobilized in abduction and internal rotation or treated in this position after failure of the frog leg position was open reduction required. Preliminary traction, usually skeletal, with a wire through the distal femur, was used in most cases.

Results

In our evaluation, a patient was considered to have an excellent result when both the clinical examination and the roentgenographic appearance were normal. With only a slight deviation from normal in either the clinical examination or the roentgenographic appearance, the result was rated good. When a hip maintained its reduction but had abnormal roentgenographic appearance or mild loss of function, the result was considered fair. Patients in these three groups were classed as having satisfactory results. When there was moderate limitation of function or the reduction was not maintained, the result was considered poor.

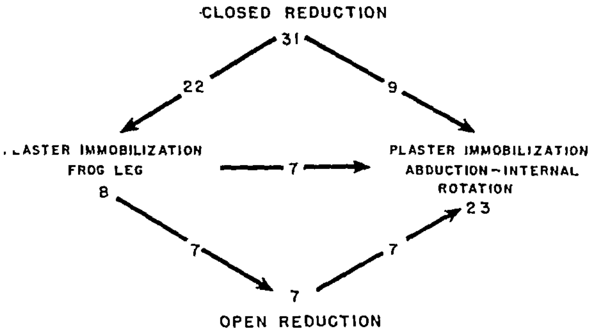
CLOSED REDUCTION
31
22
9
LASTER IMMOBILIZATION FROG LEG
8
7
PLASTER IMMOBILIZATION ABDUCTION-INTERNAL ROTATION
23
7
7
7
OPEN REDUCTION

Fig. 1.—Summary of treatment in 31 hips.

Of the 31 hips treated there were 27 satisfactory results and 4 failures. The results according to the various types of treatment used were as follows: group 1 includes those patients with hips in which closed reduction in the frog leg position was used and continued throughout the period of immobilization. This period ranged from 7 to 18 months, with an average immobilization of 9 months. No surgical attempt to correct anteversion was carried out in these patients. Although the eight hips included in this group were rated satisfactory (three excellent and five good), it should be emphasized that there were 14 other hips initially treated this way which had to have an alteration in treatment, and these failures represent groups 3 and 4.

Treatment with the frog leg position alone has not been used at Lakeville since 1954, because of the frequency of redislocation even after prolonged immobilization in a plaster cast. Our present method of treatment was used in the patients in group 2. Their nine hips were initially reduced and maintained in abduction and internal rotation. There were eight excellent results and one good result. In seven of the nine hips, a rotation osteotomy was performed in the subtrochanteric area to correct excessive anteversion. Internal fixation with a four-hole plate and screws was used to maintain the correction. The period of immobilization in this group ranged from four to eight months; a shorter period was used when immobilization was combined with corrective osteotomy.

Group 3 represents those patients in whom the frog leg position was used initially and then altered to abduction–internal rotation after failure of reduction. Five of the seven hips in this group had satisfactory and two unsatisfactory results. The two failures in this group occurred in a patient with bilateral recurrent dislocations, who has been treated in both frog leg and abduction–internal rotation positions and who continues to have dislocations anteriorly. During the past year this patient has undergone rotation osteotomies and a shelf stabilization procedure. It is too early to evaluate the results of these procedures; therefore, this patient is still considered to have a failure.

Those patients who underwent open reduction after failure of the frog leg position constitute group 4. Of their seven hips there were five satisfactory results and two failures. One patient died postoperatively, with acute pulmonary edema, and the second was transferred to a mental institution before completion of treatment.

Complications.—There were three postoperative varus deformities of the femoral neck after performance of rotation osteotomy and two failures of rotation osteotomy, one of which required a repeated correction before a satisfactory result was obtained. The second case was one of overcorrection due to a shallow acetabulum. There was one superficial postoperative wound infection in a patient after rotation osteotomy which healed without further complication. One patient developed a deep wound infection after a shelf procedure but subsequently did well and underwent another shelf operation and two rotation osteotomies without further incident. There were three cases in which the hip continued to dislocate. Two patients with such hips are undergoing treatment at the time of writing. There were three hips with mild aseptic necrosis.

Other orthopedists have used and recommended abduction with internal rotation for the position of reduction and immobilization in these cases.[1] The importance of excessive anteversion in the etiology of this condition has been previously described.[2] We have learned the hard way—by trial and error.

Report of Cases

Case 1.—A 26-month-old girl was admitted to another hospital in November, 1953, with a diagnosis of bilateral congenital dislocation of the hips. A closed reduction was successful, bilaterally, and the patient was immobilized in the frog leg position. After five months of hospitalization the patient was referred to Lakeville, with instructions to continue the immobilization for an *additional four months.* The patient was then allowed up and several months later the hips were noted to be unstable.

Examination under fluoroscopy showed the left hip to dislocate and the right hip to subluxate on external rotation, but both hips were well reduced on internal rotation. We felt that additional plaster-cast immobilization in abduction–internal rotation was needed, but the referring orthopedist insisted we repeat the frog leg position for an additional nine months. This was carried out and after ambulation was started the hips were again unstable. The treatment was then altered. After reducing the hips in abduction–internal rotation in December, 1955, a rotation osteotomy of the left femur was carried out. After five months of immobilization the patient was again allowed to walk. Her hips were stable in all positions and she was discharged from the hospital almost three years after her *initial reduction* (*fig.* 2).

Case 2.—A 17-month-old boy had a congenital dislocation of his left hip initially treated elsewhere in April, 1954. A successful closed reduction was done and the patient was immobilized in the frog leg position. Three weeks later he was transferred to Lakeville, where he was kept in a plaster cast for eight months before walking was allowed. His left hip was then found to be clinically unstable on weight-bearing and roentgenography showed progressive subluxation laterally. Excessive anteversion was proved roentgenographically. The hip was stable in abduction–internal rotation, and in May, 1955 (*at the age of 30 months*), he was again immobilized in a plaster cast, this time in abduction–internal rotation. After several months, he began physical therapy in a bivalved cast. He maintained his reduction but showed evidence of mild aseptic necrosis of the capital femoral epiphysis.

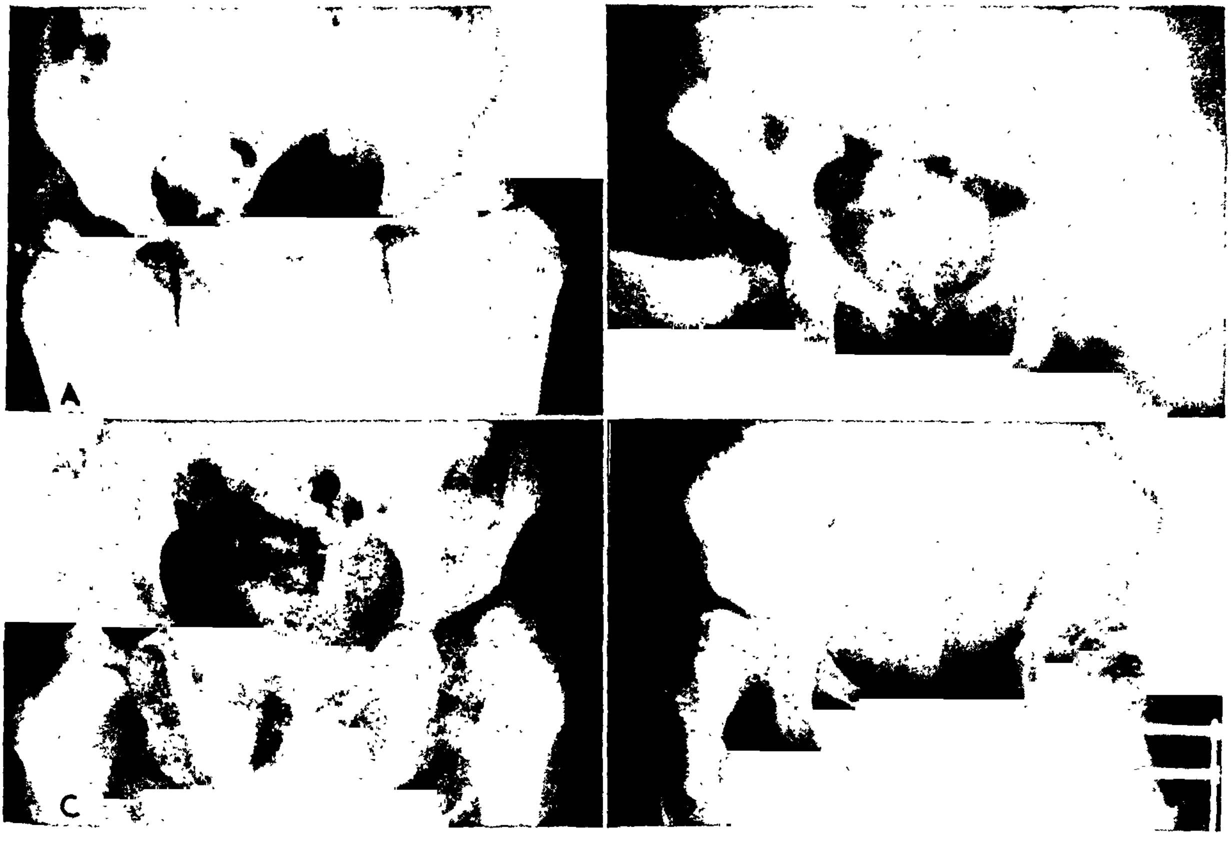

Fig. 2 (case 1).—*A*, bilateral dislocation of hips in November, 1953; *B*, successful closed reduction in frog leg position; *C*, left hip unstable on external rotation. Fluoroscopy revealed bilateral instability. Roentgenogram made after nine months' immobilization in plaster cast; *D*, alteration of treatment to abduction–internal rotation, with subtrochanteric rotation osteotomy of left femur. Hips had continued to subluxate after 18 months' immobilization in frog leg position, now are stable.

Comment.—These two cases are typical of group 3, in which patients who had failure of the frog leg position were successfully treated by changing to abduction and internal rotation. We believe the presence of excessive anteversion played an important role in these cases, and until it was managed by abduction–internal rotation and corrective osteotomy (case 1) a stable hip could not be achieved. The length of treatment could have been shortened considerably if this method of treatment had been used initially.

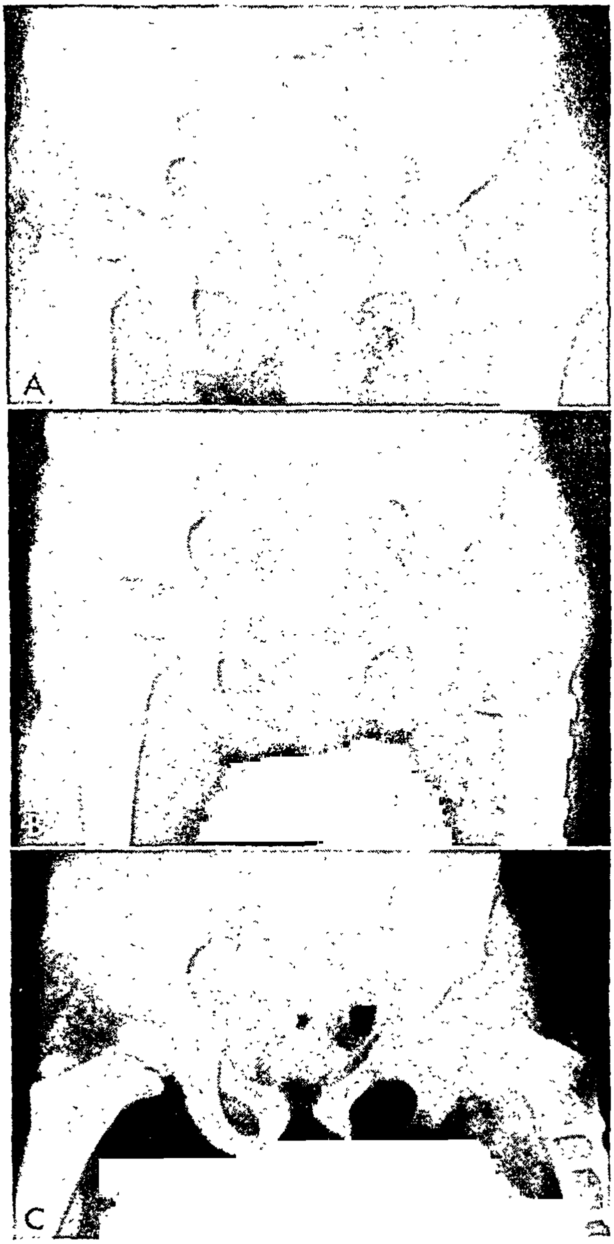

Fig. 3 (case 3).—*A*, dislocation of left hip in September, 1953; *B*, open reduction and rotation osteotomy were performed after hip redislocated, in spite of prolonged immobilization in frog leg position. Hip was still unstable in neutral position, indicating anteversion had not been corrected; *C*, after repeat rotation osteotomy with 90 degrees of correction. Anterior dislocation of hip is now stable.

Case 3.—A 15-month-old girl was given a diagnosis of congenital dislocation of the left hip after investigation of her waddling gait. In September, 1953, she was admitted to another hospital where a closed reduction and immobilization in the frog leg position was carried out. However, this was unsuccessful and another closed reduction was attempted in November, 1953. The hip continued to be unstable and in October, 1954, the patient was admitted to Lakeville, with a dislocation of the left hip still present. An open reduction was performed and at operation the anteversion was estimated to be 60 degrees. The next month a rotation osteotomy was done and the leg was immobilized in abduction–internal rotation. Several months later, however, it was noted that the hip redislocated on external rotation. This was studied by fluoroscopy and it was seen that the anteversion had not been corrected by the osteotomy. In spite of several additional months of plaster-cast immobilization in abduction and internal rotation, the hip continued to be unstable. The patient had a waddling gait but was discharged from the hospital against advice in September, 1955.

On follow-up visits the clinical and roentgenographic examination showed the hip to be unstable in neutral position but well reduced in internal rotation, which indicated that the anteversion had not been corrected. In December, 1957, the patient was readmitted to the hospital with no change in the status of the left hip. An arthrotomy was performed, with the full intention of performing a shelf-stabilization procedure, but examination under direct vision clearly demonstrated that the hip reduced easily when the leg was rotated internally. The dislocation was anterior and the anteversion was 90 degrees. A rotation osteotomy was then redone and the leg was immobilized in the appropriate position. The patient was discharged several months later with a stable hip and has continued to do well (fig. 3).

Comment.—This case is typical of group 4, in which patients were treated by open reduction after failure of frog leg position. A failure of closed reduction in the frog leg position was handled by open reduction and immobilization in abduction and internal rotation, followed by subtrochanteric rotation osteotomy. An incomplete correction of the marked femoral torsion, however, was responsible for continuation of the dislocation, necessitating a second rotation osteotomy before a stable hip was achieved.

Case 4.—At the age of 14 months a girl had a waddling gait and often fell. One month later a diagnosis of bilateral dislocation of the hips was made. The patient was admitted to Lakeville for her initial treatment in July, 1953. Reduction was possible in both frog leg and internal rotation positions. However, the patient was immobilized for seven months in the frog leg position after an excellent reduction was achieved. The follow-up roentgenograms over a three-year period showed excellent hips bilaterally. However, comparison of the neutral anteroposterior view with an anteroposterior view in internal rotation showed more stability in the latter position, indicating increased anteversion (fig. 4).

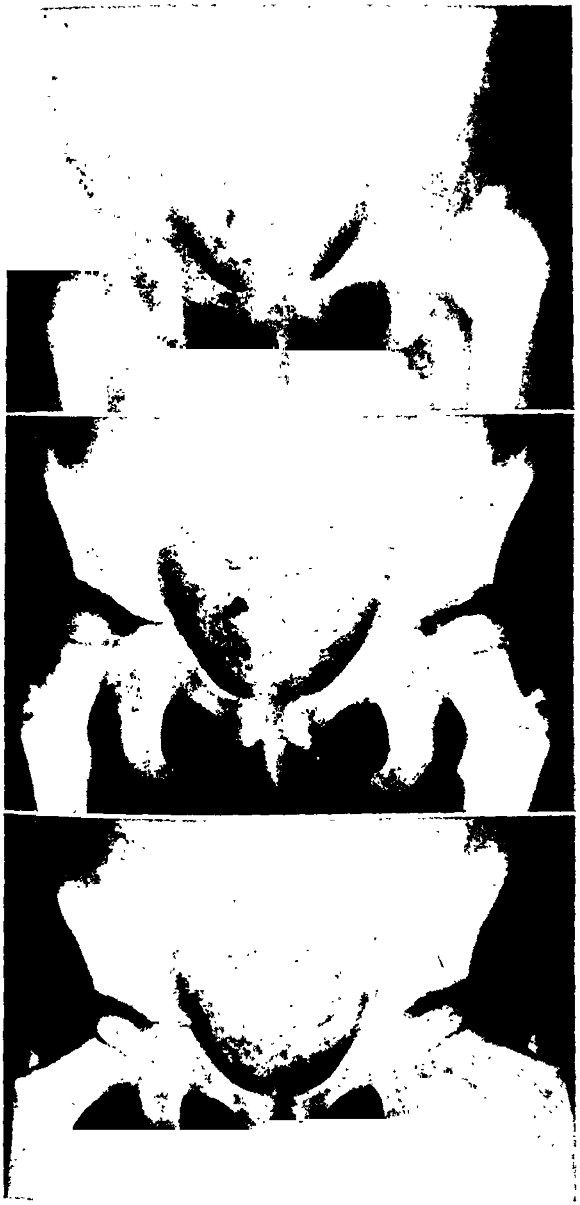

Fig. 4 (case 4).—*A*, bilateral dislocation of hips, reduced and immobilized in frog leg position; *B*, roentgenogram made on follow-up examination in neutral position; *C*, on internal rotation hips are better seated, indicating presence of uncorrected anteversion.

Comment.—This case is typical of group 1, in which the frog leg position alone was successful in achieving stable hips. This was possible only because the increase in anteversion was slight in these cases. When the increase in anteversion was moderate or excessive, this method of treatment failed. The roentgenographic appearance of the hips in group 1 is characterized by an apparent coxa valga on the neutral anteroposterior view which, in these hips, is due to uncorrected increase in anteversion. Our present method of treatment is illustrated by the following cases from group 2.

Case 5.—A girl was given a diagnosis of bilateral dislocation of the hips at the age of 30 months. Two months later, in August, 1955, she was admitted to Lakeville. Roentgenograms (true lateral view) showed excessive anteversion, especially on the right (estimated at 60 degrees). A closed reduction with the hips in abduction–internal rotation was successful. Several months later a subtrochanteric rotation osteotomy of the right femur was performed. After an additional four months in a plaster cast the patient was permitted to walk. The hips maintained the reduction, and it was decided that osteotomy of the left femur was not necessary in this case. The patient had normal hips when last examined three years later (fig. 5).

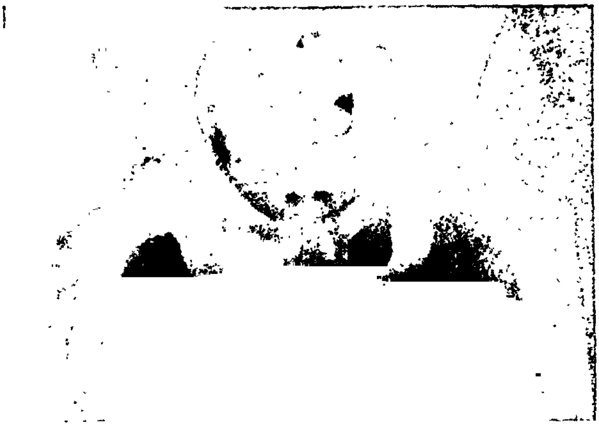

Fig. 5 (case 5).—Follow-up roentgenogram showing stable reductions in patient initially treated at the age of 32 months with closed reduction and immobilization in abduction–internal rotation. Rotation osteotomy was performed on right.

Case 6.—A boy started walking at the age of 15 months. Roentgenograms taken to evaluate his waddling gait revealed bilateral congenital dislocation of the hips. A 45-degree cephalad view showed the dislocations to be anterior. After several weeks of preliminary skin traction the hips were reduced under anesthesia in abduction and internal rotation. Five months later a subtrochanteric rotation osteotomy with 90 degrees of correction was carried out on the right. One month later, a similar procedure was done on the left. After several months he was permitted to walk and has continued to do well. Figure 6 demonstrates the original anteroposterior view and the 45-degree cephalad view which was originally described by Martz and Taylor.[3]

Comment

Anteversion and Rotation Osteotomy.—Anteversion is an important factor in the evaluation of these hips and must be considered in the management of each case. An estimate of its severity can often be made by comparing the neutral anteroposterior roentgenographic view with the anteroposterior view on internal rotation. The measurement of anteversion with use of the true lateral view alone was inaccurate in this series when compared with findings at open operation.

Patients with mild (less than 45 degrees) increase in the degree of anteversion can be satisfactorily treated in either the frog leg position or abduction internal rotation. A second group with moderate (45-60 degrees) anteversion will continue to have instability even after prolonged immobilization in the frog leg position but may be successfully treated by abduction–internal rotation. There are hips with severe degrees of anteversion (over 60 degrees) in which rotation osteotomy is necessary to achieve a stable hip.

The use of rotation osteotomy to correct anteversion is mandatory in the severe group but may also be used in the moderate group to shorten the period of postreduction immobilization. Failure to correct excessive anteversion is the most common cause of redislocation in these patients.

We prefer subtrochanteric to supracondylar osteotomy, because more correction can be obtained at this site and we believe that this is important, especially in anterior dislocations which are associated with severe anteversion, even in excess of 90 degrees.

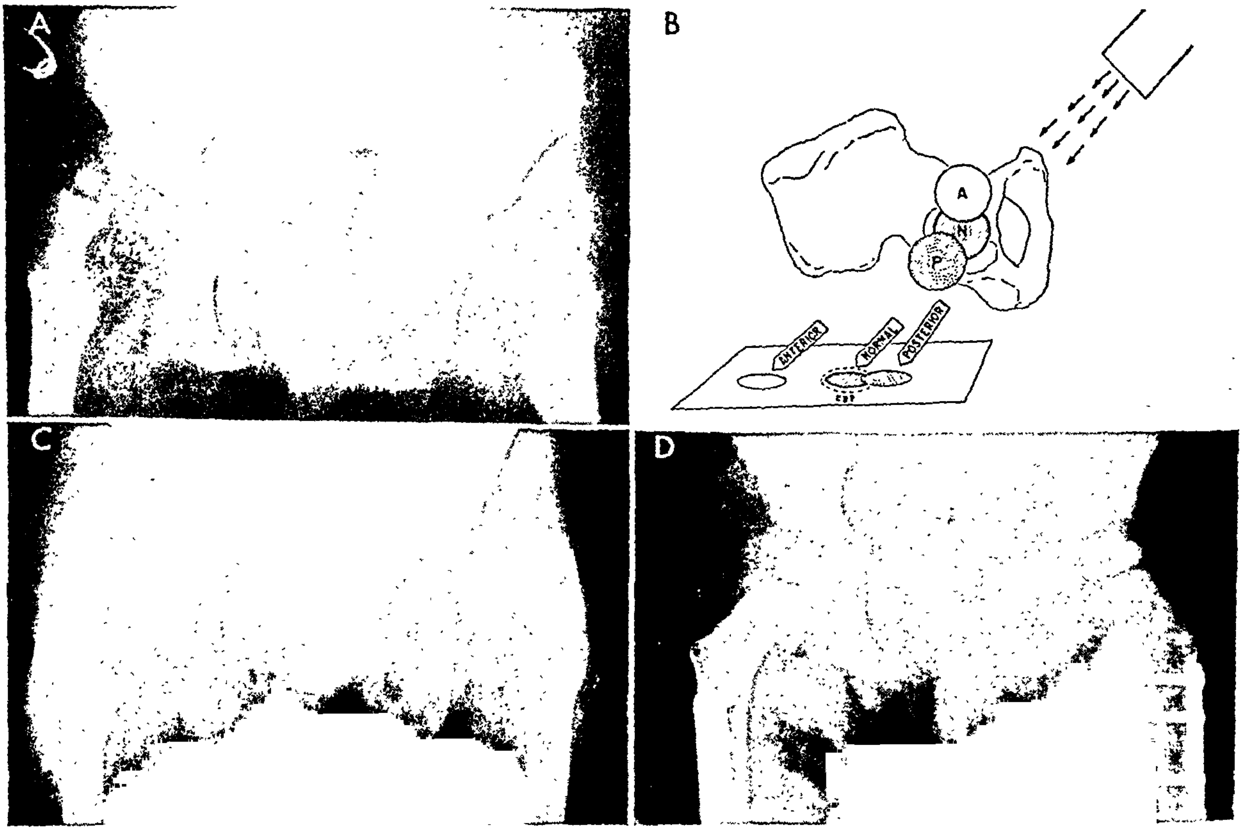

Fig. 6 (case 6).—*A*, bilateral dislocation of hips; *B*, 45-degree cephalad view; *C*, roentgenogram of 45-degree cephalad view. Hips are projected anteriorly, indicating anterior dislocation; *D*, stable hips after closed reduction and rotation osteotomies.

Position of Immobilization.—The position of immobilization after closed reduction is controversial. We believe that abduction–internal rotation is preferred, because it not only achieves a stable reduction but also gives a good estimate of the anteversion as indicated by the amount of internal rotation necessary to achieve stability. With moderate or severe increases in anteversion, corrective osteotomy should be performed to prevent recurrent dislocation and to shorten the period of immobilization.

Occasionally, reduction will be achieved only in the frog leg position, and this should be used initially with a plan to change gradually to internal rotation when the cast is changed. The need for osteotomy in these cases may be determined by the same criteria as described above after the final position of internal rotation is achieved.

Initial Examination.—The initial examination of these patients should follow some orderly pattern, because the x-ray exposure for many of these children was excessive. The following views would provide the necessary information on initial roentgenographic examination: an anteroposterior view in neutral and internal rotation, a true lateral view to aid in the measurement of anteversion,[4] and a 45-degree cephalad[3] view to determine whether *the dislocation is anterior or posterior.* The frequency of anterior dislocations was not appreciated by us until we began using this view. This roentgenogram is easy to interpret, because a superior projection of the femoral head indicates an anterior dislocation, while an inferior projection indicates a posterior dislocation (see fig. 6*B*).

Open Reduction.—Recently Somerville and Scott[5] have stressed the advisability of early open reduction in these cases. Although almost one-quarter of the hips in this series had open reductions, they represent our early efforts. With our present method of treatment, open reduction has not often been necessary. We believe that it is indicated only if a closed reduction is not possible.

Summary and Conclusions

We hope that the day is near when the group of patients with congenital dislocations of the hip, a potentially crippling condition, will be diagnosed during infancy before they begin to walk. Until then it is the responsibility of the orthopedist to treat this group of patients well. An initial closed reduction followed by immobilization in abduction-internal rotation and combined with rotation osteotomy in selected cases has consistently given us a high percentage of satisfactory results. Therefore, we recommend this treatment as the preferred method in this age group.

6 Parkway Rd., Brookline (Dr. Nalebuff).

Mr. Leonard Shaffer, photographer of the Veterans Administration Hospital, cooperated in the preparation of the illustrations.

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LABORATORY ANIMALS FOR THE STUDY OF OSTEOARTHRITIS.—Osteoarthritis is a widely prevalent disorder in man and bulky mammals, and has been noted in large fossil reptiles. Its occurrence in small laboratory animals was not recognized until recent years. In a survey of wild mammals, Fox studied the joints from 173 rodents. In none was arthritis apparent. This investigator cited a communication from Dr. Hamerton of the London Zoological Society, in which he stated that he had had a similar experience in a study of arthritis over a period of 15 years. Nevertheless, Silberberg and Silberberg demonstrated that osteoarthritis of microscopic proportion does indeed occur in mice under certain conditions. Osteoarthritis is generally believed to arise from mechanical erosion of the articulating surfaces of the movable joints and, for this reason, to be a wear-and-tear phenomenon—whether from the insidious abrasion of everyday weight-bearing or, in its acute form, from trauma or mechanical disadvantage. If this is true there would appear to be little prospect for preventing or ameliorating this exceedingly common and economically destructive disease of man and livestock. . . . Osteoarthritis of small laboratory animals closely simulates its counterpart in man and livestock. The studies indicate that local factors profoundly affect its development. Genetic factors also are important, although it is not clear whether they operate at a local level or in some more general constitutional manner. The observations provide encouragement and a tool for examining the possibility that environmental factors contribute appreciably to the development, and therefore potentially to the control, of this economically destructive rheumatic disorder.—L. Sokoloff, M.D., Osteoarthritis in Laboratory Animals, *Laboratory Investigation*, November-December, 1959.

VESICOURETERAL REFLUX IN CHILDREN

Victor A. Politano, M.D., Durham, N. C.

Vesicoureteral reflux, the regurgitation of urine from the bladder back into the ureters, is considered abnormal regardless of the age group in which it appears. The author believes that, if it is allowed to continue, it will inevitably destroy the kidney and that, once the diagnosis has been established, the process should be eliminated. The more conservative methods of urethral dilatations, multiple voidings, indwelling catheters, or various modifications of the vesical outlet should be tried if indications for such measures exist. Ureteral reimplantation by creation of a submucosal tunnel was found necessary in 17 girls and 9 boys in the author's series. All had had recurrent urinary tract infections, and several had progressed to various stages of uremia. These operations have given excellent anatomic and clinical results.

Vesicoureteral reflux, the regurgitation of urine after it has entered the bladder back into the ureter, has been a topic of intense interest and speculation. Pozzi,[1] in 1891, noted urine coming from both ends of a cut ureter. Modlinsky[2] noted cessation of urine passage through the urethra and passage of urine through the lumbar incision after nephrectomy for hydronephrosis. Kelly[3] described reflux of air on several occasions during air cystoscopy in patients with inflamed ureteral orifices. These observations resulted in extensive investigations into the frequency with which ureteral reflux occurred and the conditions necessary for its occurrence. Graves and Davidoff[4] demonstrated reflux in 86% of rabbits studied. Wislocki and O'Conor[5] made similar observations. Most of the early experimental studies were done in rabbits, and conclusions from these studies about the competency of the ureterovesical sphincter in animals were thought to apply to man. Sampson,[6] in an exhaustive treatise on urinary infections and the role of reflux in ascending infections, theorized that the length and obliquity of the intramural ureter was an important factor. It was left for Gruber[7] to do a comparative study in animals and human beings and illustrate that the percentage of ureteral reflux varied inversely with the thickness of the bladder and length of intravesical ureter. In rabbits reflux occurred in as many as 80%, but the rate rapidly decreased toward zero as animals with thicker bladders, more prominent development of the trigonum vesicae and the muscli pylari of the ureters (Bell's muscle), and increased length of the intravesical ureter were used. The human bladder showed the highest development of these structures and did not demonstrate reflux. Gruber observed that the intravesical ureter is not a sphincter dependent on muscle tone or muscle contraction but acts passively and serves as a true valve, one flap only being mobile, the other being the bladder wall itself. An increase in intravesical pressure presses the valve more closely against the bladder wall and prevents reflux of fluid.

With the passing of many of the early investigators, interest waned, and for many years vesicoureteral reflux was treated rather passively. In recent years there has been a resurgence of interest in this problem. It is becoming more evident that ureteral reflux in the presence of infection and progressive ureteral dilatation will lead to impairment of renal function and ultimate total renal destruction. In spite of this fact, a direct positive approach to correction of the problem is often tempered by conflicting opinions about whether reflux may occur in a normal child. Graves and Davidoff suggest that the contraction force of the bladder may produce reflux in the presence of normal ureterovesical valves in man. Gibson[8] studied 43 children without urological complaints by cystograms and observed reflux in 2. From this study he concluded that "ureteral reflux may occur in children who have apparently normal urological tracts." This conclusion was drawn without further explanation or investigation of the two children that demonstrated this condition. Bumpus[9] stated, "I have not known it to occur if the bladder was normal, except in children." No reference was made to any studies conducted in children or to any other basis for such a statement. Others[10] do not share this opinion.

Occurrence

Campbell[10a] surveyed 722 cystograms done in infants and children and was unable to demonstrate reflux in the absence of other associated urologic problems. Jones and Headstream,[11] in a study of 100 normal children ranging in ages from 14 days to 14 years demonstrated reflux in only 1. The one child with reflux was found to be carrying 180 cc. of residual urine and was treated by transurethral resection of the vesical neck. Bunge[12] examined 24 normal children and adults ranging in age from 9 months to 74 years. Ureteral reflux did not appear in any of the examinations. In our own study of over 50 normal children, ureteral reflux was not demonstrated in a single case. The absence of reflux in normal children is impressive when com-

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From the Department of Urology, Duke University School of Medicine.

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pared to the frequency with which it occurs in persons with other urologic lesions. Bumpus observed reflux in 8.6% of cystograms showing other urologic problems. Twelve per cent of the cystograms reviewed by Campbell demonstrated reflux in children with coexisting urologic diseases. St. Martin, Campbell, and Pesquier [16] noted reflux in 13.5% of children investigated because of urologic symptoms. Roughly 10 to 12% of children with urologic complaints can be expected to demonstrate vesicoureteral reflux.

Diagnosis

The diagnosis is usually simple to make and is demonstrated by cystography. Talbot and Bunts,[13] in 1949, emphasized the importance of delayed cystograms for demonstrating ureteral reflux. Voiding cystourethrograms will increase the incidence by which reflux can be demonstrated. The cystogram is obtained by injecting from 30 to 90 cc., depending on the size of the child, of methiodal sodium (Skiodan) or a similar contrast substance through a small urethral catheter./The catheter is removed, and in 20 or 30 minutes the child is instructed to void. An x-ray film is taken while he is voiding. In the very young or unco-operative child the same results can be expected if he is made to cry. It is important to repeat the cystograms on several occasions if ureteral reflux is suspected and is not demonstrated in the first cystogram or if reflux is demonstrated in one side only. Not infrequently, even in the presence of large, patulous ureteral orifices and dilated ureters, reflux may not be demonstrated or may be visualized in one side only at any given examination. Cystograms are essential to any complete urologic study in a child, and vesicoureteral reflux must be suspected in any child with repeated urinary tract infections, residual urine, unexplained fevers, flank pain, or vague abdominal complaints. There is a tendency to eliminate this valuable diagnostic procedure when intravenous pyelograms show normal findings. It must be remembered that about 60 to 70% of patients that demonstrate vesicoureteral reflux, even with advanced changes, will show essentially normal results in intravenous pyelograms.

Etiology

Several factors may produce or be responsible for the occurrence of vesicoureteral reflux. Infection, which is present in many instances and is often the presenting complaint, may produce fibrosis and fixation of the ureter with loss of elasticity of the intramural portion, thus interfering with its normal function. Ureteral reflux is frequently seen with neurological disorders of the bladder and especially in cord injuries. Congenital anomalies, such as ectopic ureteral orifices or developmental deformities of the trigone, may be a cause. Trauma to the intramural ureter incident to surgery of ureteroceles, meatotomies, or transurethral resections is a well-recognized cause for reflux. It is commonly seen in children with obstructions to the vesical outlet—such as contractures, median bars, posterior urethral valves, or strictures. Yet reflux is not a frequent observation in adults with obstructive disease. It is often extremely difficult and at times impossible to clinically demonstrate any evidence of obstruction to the bladder outlet in children that demonstrate ureteral regurgitation. This strongly suggests some intrinsic defect or weakness of the intravesical ureter or vesicoureteral valve such as a thin-walled bladder with a short intramural ureter or poorly developed muscli pylori of the ureters or trigonum vesicae, or any combination of these. The defect, whatever it is, is sufficient to prevent the valve from withstanding normal intravesical pressure variants.

Management

Once the diagnosis has been established, every effort should be made to eliminate the process, which if allowed to continue will inevitably destroy the kidney. Infections should be eradicated. This may be difficult or even impossible in the presence of large, dilated, tortuous ureters or with residual urine. Neurogenic disorders should be corrected or modified with appropriate drug therapy when possible or modified by surgical methods when feasible. Residual urine secondary to vesical neck obstructions must be eliminated. Some children may be improved by multiple voidings, others may improve with urethral dilatations, while still others may need transurethral resections or open modifications of the vesical outlet. Every conservative effort to eliminate reflux should be attempted first. If these measures fail to resolve or improve the problem and if there is progressive loss of renal function due to either repeated infections or progressive dilatation, a direct attack on the intramural ureter may be necessary. The creation of a submucosal tunnel described by Politano and Leadbetter[11] has been most successful in correcting vesicoureteral reflux without producing obstruction to the efflux of urine.

Ureteral Reimplantations and Results

Ureteral reimplantations by creation of a submucosal tunnel has been performed in 26 children with vesicoureteral reflux during the past four years. Reimplantation was considered essential in these patients for one of several reasons. All had recurrent urinary tract infections lasting for periods ranging from six months to as long as four years. Many showed signs of impaired renal function as evidenced by a depressed phenosulfonphthalein test value, elevated blood urea nitrogen level, or radiographic changes consistent with pyelonephritis. Several had progressed to stages of uremia. All had been given antibacterial drug therapy for varying lengths of time, several over protracted periods, only to relapse with discontinuance of drug therapy. Surgery, either in the form of urethral dilatations or modification of the vesical neck, had been done on a few of the patients without improvement in symptoms. Nephrectomy without relief of symptoms had been performed on one child. It was necessary to do nephrectomies on two other children after correction of reflux in the better kidney. Of the 26 children treated there were 17 girls and 9 boys. In eight boys and in nine girls both ureters were involved. In one boy and in three girls the right ureter alone was involved. In seven girls only the left ureter was involved. No boys had involvement of the left ureter only. Ten children have previously had or had at the time of their reimplantation transurethral resection or YV-plasty of the bladder outlet. Of these, six were boys and four were girls.

Modification of the vesical outlet was not considered necessary in the remainder. Eight of nine boys had bilateral reflux, and surgical modification of the vesical neck was considered necessary in six. Only 3 of 17 girls were thought to have a degree of bladder neck obstruction. Unilateral reflux occurred about as commonly as bilateral in the girls.

There has been one complete failure and one partial failure in the 26 children in whom reimplantation for vesicoureteral reflux was done. The complete failure was in a boy who had undergone several surgical procedures prior to reimplantation of his ureters. These consisted of transurethral resection of posterior urethral valves, suprapubic cystostomy, bilateral nephrostomies, and mobilization and resection of a long segment of large, dilated, tortuous ureters with a direct reimplantation. During the submucosal reimplantation the ureters were found to be thick, fibrotic, and partially rigid. This child has been given constant suprapubic catheter drainage since reimplantation, and there has been improvement in the degree of reflux with the lapse of time. The partial failure was in a child with advanced bilateral pyelonephritis and a four-year history of repeated infections. After reimplantation ureteral reflux persisted on the right side for about six months but has since disappeared. Reimplantations by creation of a submucosal tunnel have been done for conditions other than ureteral reflux. These conditions include segmental resection of the bladder in which the trigonum vesicae has been sacrificed, low ureteral strictures, ureterovesical strictures, congenital megalo ureters, and reflux secondary to trauma of the intravesical ureter. It is not within the scope of this paper to cover these conditions, many of which occurred in adults.

In the successful reimplantations there have been no evidences of obstruction to the upper tract, which indicates free efflux of urine through the newly-created intravesical ureter. All children have remained asymptomatic, in most of them renal function has improved, and urine samples are sterile.

Increasing experience with this problem strongly suggests that vesicoureteral reflux is an abnormal finding which children do not outgrow. Bumpus found reflux present in 19% of patients with pyelonephritis. A number of adults which I have studied with advanced or terminal pyelonephritis have demonstrated a free regurgitation of vesical contents to the kidneys. Had these adults had undiagnosed or unrecognized vesicoureteral reflux when they were children? One can only speculate about the answer.

Report of a Case

A 4-year-old girl was admitted with a five-month history of intermittent fever with temperature elevations to 105 F (40.6 C) occurring every three to four days. She had mild irritative symptoms on voiding, consisting of burning and frequency. Her fever was controlled with sulfisoxazole (Gantrisin), which she had been taking for six weeks prior to admission.

On physical examination her temperature was 100.2 F (77.8 C) pulse rate 90 per minute, respirations 25 per minute, and blood pressure 98 mm. Hg systolic and 76 mm. Hg diastolic. She was a small but normally developed child. Laboratory studies showed a hemoglobin level of 12.6 Gm. with a white blood cell count of 11,000 per cubic milimeter. Urinalysis showed 20 to 25 white blood cells and 10 red blood cells per high-power field. The nonprotein nitrogen level was 34 mg. per 100 cc.

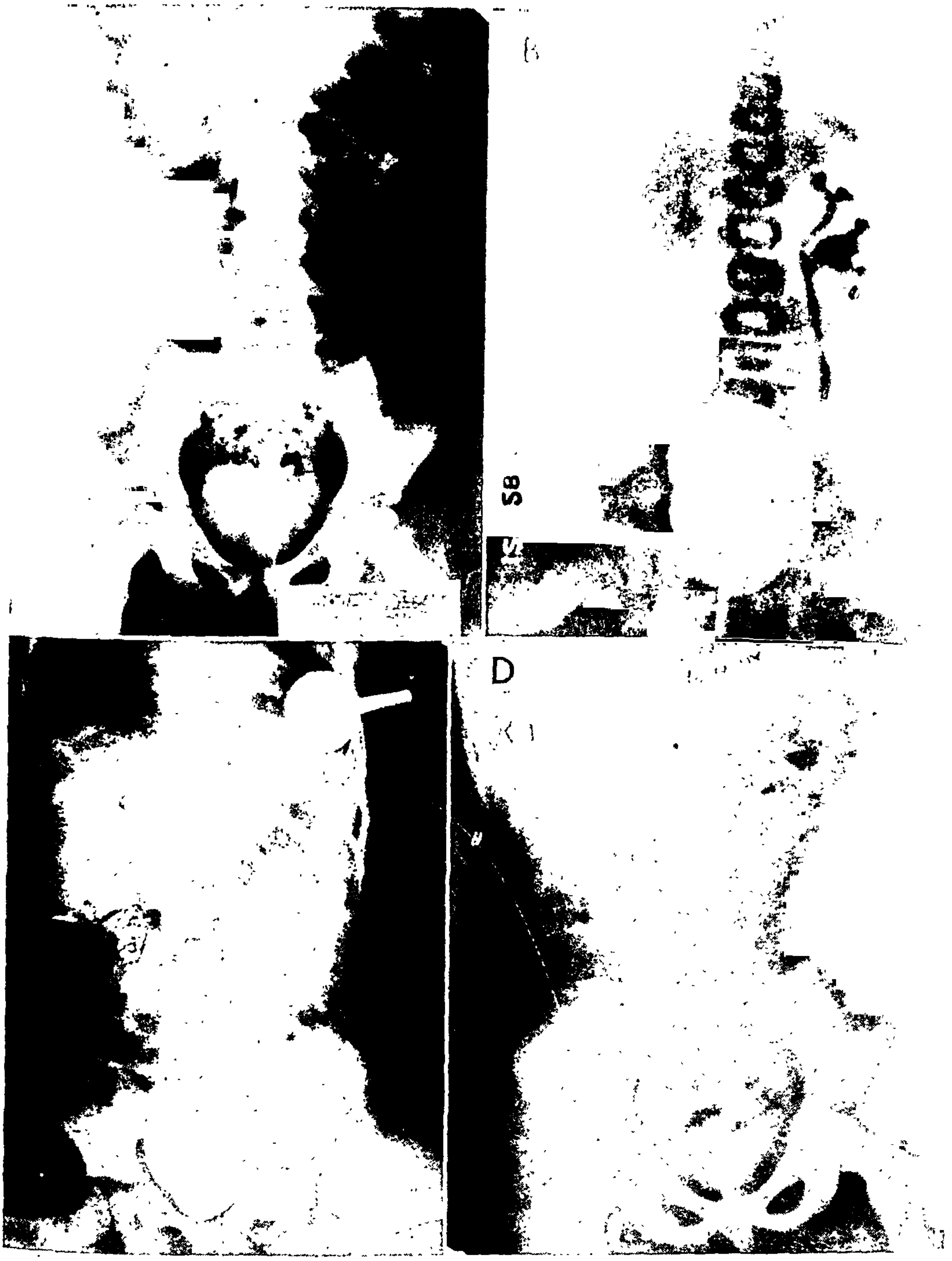
Intravenous pyelograms (see figure, part *A*) showed slight hydronephrosis of a double left kidney with blunting of the calyces. There was partial reduplication of the left ureter. A cystogram (see figure, part *B*) demonstrated immediate ureteral reflux on the left. On cystoscopic examination the left ureteral orifice was found to be lateral to the trigonum vesicae high on the left lateral portion of the bladder wall. The right ureteral orifice was in its normal anatomic position. The bladder outlet was considered normal. The diagnosis was ectopic ureteral insertion with ureteral reflux and pyelonephritis on the left side.

Treatment consisted of reimplantation of the left ureter by creation of a submucosal tunnel. This successfully corrected the vesicoureteral reflux (see figure, part *C*). Postoperative intravenous pyelograms showed good excretion from the left kidney without evidence of obstruction (see figure, part *D*). The child has remained asymptomatic for a period of 40 months. Microscopic examination of urine showed negative results, and cultures have been sterile.

Summary

Vesicoureteral reflux is an abnormal finding regardless of the age group in which it appears. This condition, if unrecognized and untreated, may lead to severe renal damage and ultimate renal destruction because of repeated infections and progressive dilatation. Cystograms should be a part of every complete urologic investigation in children. Once the condition is recognized, immediate treatment should be instituted to eliminate this problem. The more conservative methods of urethral dilatation

tiple voidings, indwelling catheters, or various ifications of the vesical outlet should be tried indications for such measures are present. If these nservative methods fail to correct the problem, a direct attack on the intravesical ureter should be de. There probably exists some inherent defect or weakness in the vesicoureteral valve which permits reflux to occur *with normal or slightly elevated* intravesical pressures. Reimplantation of the ureter through a submucosal tunnel performed in 26 children has given excellent anatomic and clinical results.



Findings in 4-year-old girl with vesicoureteral reflux. *A*, preoperative intravenous pyelograms show blunting of calyces *on left with bifid kidney and ureter*. *B*, preoperative cystogram shows reflux on left, and contrast medium in right pelvis represents continued excretion from contrast medium after intravenous pyelograms had been made. *C*, postoperative cystogram demonstrates absence of reflux. *D*, postoperative intravenous pyelogram shows essentially same calyceal pattern as preoperative films.

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DEVELOPMENT OF URINARY CONTROL IN CHILDREN

SOME ASPECTS OF THE CAUSE AND TREATMENT OF PRIMARY ENURESIS

S. Richard Muellner, M.D., Boston

A study of the development of urinary control in 1,000 children confirmed the belief that bladder control is a self-learned skill, which most children acquire by the age of 4½ years. In the acquisition of urinary control the child learns to coordinate the use of the levator ani, the thoracic diaphragm, and the abdominal musculature, which constitute the "voluntary mechanism" of urination in the adult. Through the use of the "voluntary mechanism" the child doubles its bladder capacity by the age of 4½ as compared to what it was at the age of 2 years. The enlarged bladder capacity insures night control of the urine. Children who fail to enlarge their bladder capacity become enuretic. The author believes that a potential enuretic can be recognized by the age of 3 years. A simple program which can be used to prevent and to eliminate bedwetting is described.

An infant starts life with an automatic bladder. By the time a child is 4½ years old, it has acquired complete urinary control both by day and by night. Our studies show that if this maturation process, which occurs between the ages of 2 and 4½ years, is incomplete, the child will be left with a bladder which retains some of its infantile characteristics and will have improper urinary control or enuresis. What, precisely, happens in this short span to bring about this profound change in the function of the bladder is important if we are to understand the genesis of enuresis and its rational treatment.

The impression is widely held that the acquisition of normal urinary control is due to parental training, whereby conditioned reflexes are established by means of some mysterious maturation of the autonomic nervous system. This theory and similar theories about the nature of the development of urinary control in children are quite vague and leave many questions unanswered. My recent studies of the physiology of micturition by means of the fluoroscope—a technique which by now has been employed in over 1,000 cases, encompassing all sorts of micturition problems as well as measurements of the capacity of the bladder in the infant, in the normal child, and in the enuretic child—have clearly shown that the acquisition of adult bladder

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From the Department of Surgery (Urology), Harvard Medical School, and Department of Urology, Beth Israel Hospital.

control is due to a self-learned skill in the use of large skeletal muscle groups with which the child manipulates its intra-abdominal pressure.

Klackenberg,[1] in a careful study of 315 children, aged 1 to 7 years, showed conclusively that there is no correlation between parental "training" efforts and the development of urinary control. Others have offered similar proof that urinary control is not something that the child is taught by its parents but that, on the contrary, it is a process which each child develops at its own pace, irrespective of parental travail.

Steps in Development

A review of the steps which the child must take to change from an infantile to an adult type of bladder control will show the nature and the complexity of this process, which is usually taken for granted. It will then become apparent why things can and do go wrong with this process.

The infant voids automatically, i. e., the detrusor contracts spontaneously when its limit is reached and maintains this contraction until the bladder empties. The child appears to have no sensation of bladder fulness nor does it manifest any sign that it is about to void. Many a new mother has been surprised by a warm jet while her baby boy smiles at her, giving no indication that he has to void or that he is about to do so. At this stage, the infant can neither initiate nor stop the urinary stream at will. This type of micturition can be termed "detrusor micturition" in that it is based mainly on the stretch reflex and activity of the detrusor.

The next step in the development of urinary control is the child's ability to indicate that his bladder is full or that micturition is imminent. This occurs between the ages of 1 and 2 years, during which time the child gradually also acquires day control of its urine. By the age of 2 years important changes have already occurred in the developmental process: first, awareness of the full bladder and, second, the ability to "hold" urine for a brief period beyond this point. The child still cannot initiate its urinary stream at will, nor can it void when the bladder is less than full. The ability to hold urine gradually becomes more pronounced, so that in the 3-year-old child the bladder capacity steadily increases and day control becomes quite well established. By the age of 4½ years most children are able to control their urine during the night as well. Bloomfield and Douglas[2] have shown that 87.8% of 4½-year-olds have complete urinary control and 12.2% still have enuresis.

Most children aged 4½ years can stop the urinary stream at will, but they may still have some difficulty in initiating micturition at any degree of bladder filling. The exact age at which a child is able to do so varies considerably, although as a rule it will occur somewhere between the ages of 3½ and 6 years.

By the age of 4½ years, then, the following significant changes have occurred. The child no longer has an automatic bladder. The bladder capacity has become double what it was at the age of 2 years, and the child has acquired the ability to stop and to start its urinary stream at will. (All the time data given here are relative and not absolute, because children vary in the speed with which they acquire specific skills, grow, and mature.)

To understand how this remarkable process came about, it will be necessary at this point to review the mechanism of voluntary control of micturition in the adult, for that is precisely what the child has now achieved (fig. 1).

Man's ability to void at any degree of bladder filling is a unique biological phenonemon which no other mammal manifests. An apparent exception is the male dog (and other canines) who is able to deposit small amounts of urine at each pillar and post. The mechanism of micturition in the dog, however, is entirely different from that in man. In the male dog the frequent squirting of small amounts of urine is a sexually linked and hormonally controlled act that is more closely related to the sex drive than to the ordinary function of micturition.[3]

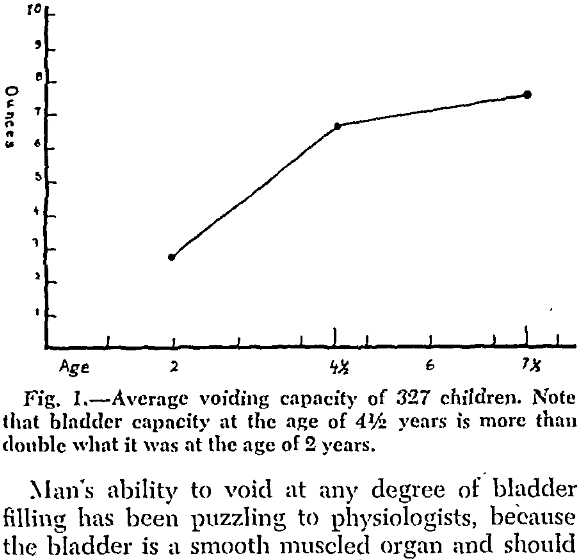

Fig. 1.—Average voiding capacity of 327 children. Note that bladder capacity at the age of 4½ years is more than double what it was at the age of 2 years.

Man's ability to void at any degree of bladder filling has been puzzling to physiologists, because the bladder is a smooth muscled organ and should not respond to the whims of the will. It had been established that the detrusor must contract for micturition to begin, but how the detrusor is made to do so by man's will was not clearly understood.

Physiology of Bladder Control

In the past, man's ability to void at any time was explained by the theory that the detrusor will automatically contract, once the acquired inhibition to its contraction is removed.[4] Studies of micturition by means of the fluoroscope, however, have shown that contraction of the detrusor is the second step in voluntary control and that it is not brought about by the direct exercise of the will over the detrusor. We found that the first step in the voluntary initiation of the urinary stream consists of the descent of the vesical neck, after which the detrusor contracts.[5] The descent of the vesical neck is brought about in the following manner. The diaphragm is fixed at the end of a brief inspiration; the lower abdominal musculature is contracted and the pubococcygeus (the anterior half of the levator ani) is relaxed. By means of the manipulation of these three large muscle groups, the intra-abdominal pressure is directed precisely toward the vesical neck and since the vesical neck support (the pubococcygeus) is relaxed, the vesical neck descends in the pelvis. It is this downward push on the vesical neck that is the stimulus for the contraction of the detrusor. The wave of contraction starts at the vesical neck and then spreads upward to the sides and dome of the bladder. The contraction of the detrusor results in the opening of the internal sphincter and micturition proceeds.

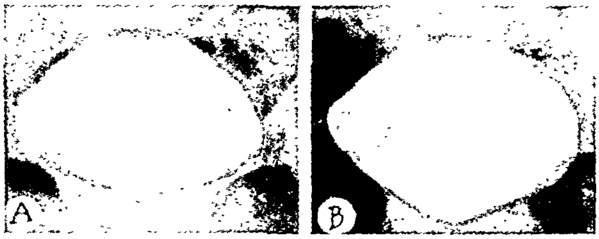

Fig. 2.—*A*, bladder at rest; *B*, first step in voluntary micturition. Note descent of vesical neck.

These findings mean that man does not have direct control over his bladder but that he uses large skeletal muscle groups over which he has full control to influence a smooth (involuntary) muscled organ. The child, therefore, must acquire the necessary skill to manipulate its intra-abdominal pressure. It is not sufficiently appreciated that, by a different application of these same muscles, man directs his intra-abdominal pressure toward the rectum to defecate and upward to the diaphragm to clear his air passages, and that he steadies all three muscle groups when he must lift heavy objects so that he will not lose his urine or his stool in doing so. I have termed the three muscle groups (diaphragm, abdominal musculature, and levator ani) with which man initiates a detrusor contraction his "voluntary mechanism" (see fig. 2, 3, and 4).

In the child the excursion of the vesical neck to initiate the urinary stream is small and rapid, and the contraction of the detrusor occurs promptly, so that the bladder quickly assumes a spherical shape in contrast to the scutiform shape it had during repose.

The first step away from infantile bladder control is the development of the cognizance of the full bladder, i. e., the desire to void, which is clearly the function of the maturing autonomic nervous system. Before long the child is able to communicate this sensation as well. The second step in the development of urinary control is the ability to hold urine for a brief period "beyond" the desire to void. To do so, the child learns to inhibit a detrusor contraction through the use of the levator ani. This, then, is the second step in the maturation process, although it constitutes the first attempt which the child makes to use one of the large skeletal muscle groups. The third step is the ability to start the stream when the bladder is full or nearly so. Here the diaphragm and abdominal muscles are first used to create and direct the intra-abdominal pressure toward the bladder. Being still quite sensitive to stretch at this stage, the detrusor requires little intra-abdominal pressure for contraction. *At this stage, the child cannot as yet start* his urinary stream at any degree of bladder filling. This comes much later, for to do this, he must now develop the coordinate use of all three muscle groups; i. e., the diaphragm, the abdominal muscles, and the levator ani, including the separate use of the pubococcygeus. The child must contract the former two and relax the latter at the same time, in order to get the detrusor to contract at any degree of bladder filling. This last step is the most difficult and is the final step in the change-over from the infantile to the adult type of bladder control.

Just as the child's initial efforts at walking are uncertain and awkward, so are his early attempts to manipulate his intra-abdominal pressure. The small boy at first stands at the toilet bowl, arches his back, and balloons out his abdomen, without being able to initiate the reflexes of micturition. After a considerable effort to do so, he announces he cannot, only to wet spontaneously a few minutes later. Through trial and error he learns that ballooning his abdomen is not the way to start his stream, and only gradually does he acquire the skill to direct his intra-abdominal pressure toward the bladder neck. The ability to stop the urinary stream comes easier. To do this, he does not simply contract his external sphincter, as has been taught in the past. Instead, he contracts the entire levator ani, including the pubococcygeus, and lifts the bladder neck away from the membraneous urethra, thus coapting the urethral walls over an area longer than the height of the external sphincter alone. In this manner the child shuts off his stream while the detrusor relaxes. It is only when he has learned to use his voluntary mechanism with skill and precision that he achieves complete mastery over his detrusor (fig. 3*B*).

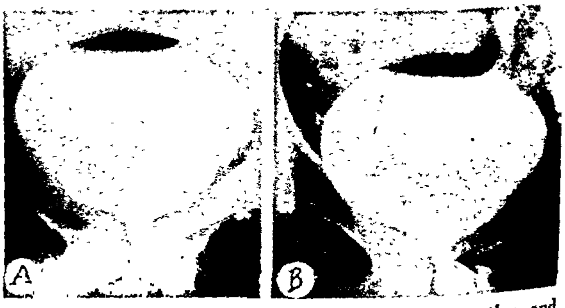

Fig. 3.—*A*, bladder during micturition; *B*, urethra and bladder at moment of voluntary inhibition of urinary stream.

Parental training constitutes at most an artificial urinary frequency which succeeds in catching the urine in the toilet bowl before the child wets its diaper. It is not possible for any parent to teach the child the complex use of the various muscle groups or to coordinate them in such a fashion as to develop mastery over the voluntary mechanism. Klackenberg's conclusion that there is no correlation between the development of urinary control and parental training is, therefore, borne out in this study.

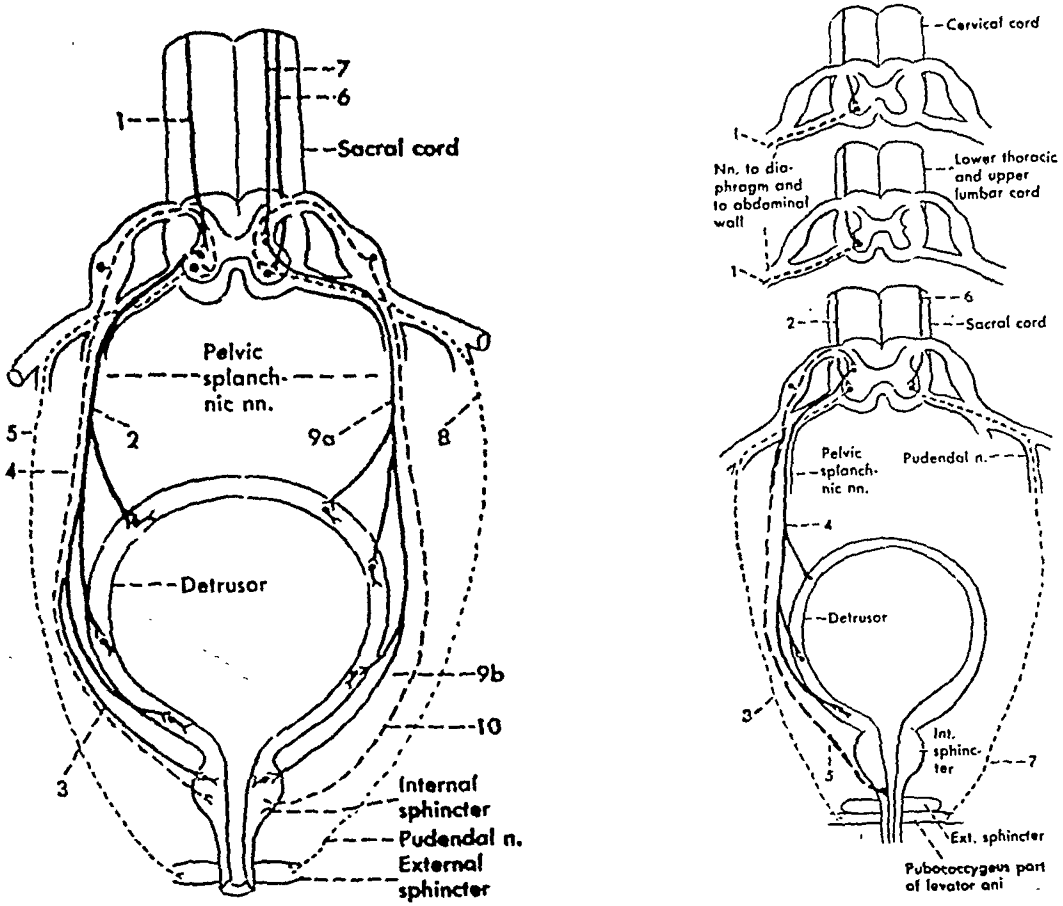

Fig. 4.—*Left,* Schema of neuromuscular mechanism for voluntary control of micturition implied by, *left,* concept of direct voluntary control over detrusor of bladder and of voluntary and reflex contraction but no inhibition of external sphincter. Initiation of micturition (*far left*): Impulses from cord, *1-2,* activate preganglionic neurons to detrusor and cause it to contract. Urination is stopped (*right*), through direct voluntary fibers, *6,* in spinal cord which activate lower motor neurons, *8,* to external urethral sphincter. Solid lines indicate descending fibers; heavy broken lines, afferent fibers; light broken lines, voluntary motor fibers. *Right,* neuromuscular mechanism for voluntary control of micturition implied by author's concept. Comparison with *left* shows that while same branches of sacral nerves are involved, mechanism is otherwise quite different. Initiation of micturition (*left side*) through voluntary contraction of abdominal musculature and thoracic diaphragm through their nerves: *1,* pubococcygeus is relaxed through descending fibers, *2,* acting on lower motor neurons, *3,* resulting in downward movement of vesical neck and initiation of detrusor contraction. Micturition is stopped (*far right*) through pyramidal tract fibers, *6,* which act on lower motor neurons of pudendal nerve, *7,* thus producing contraction of levator ani (see text for manner in which this inhibits urinary stream). (Reprinted with permission from Hollingshead, W. H.: Anatomy for Surgeons, New York, Paul B. Hoeber Inc., 1956.)

Having achieved voluntary control over his bladder, the child now can control his bladder capacity as well; he has the means at hand to enlarge this capacity to the point where the bladder will be able to hold the total output of night urine. Earlier he has achieved the ability to inhibit a detrusor contraction when the bladder is full during the day so that he can reach the toilet in time.

Elimination of Enuresis

Cause of Enuresis.—Measurements of the bladder capacity of 327 children aged from 2 to 7 years (fig. 1) have shown that when the child can hold 10 to 12 oz. (284 to 340 Gm.) of urine he will not wet at night once complete mastery of the "voluntary mechanism" has been achieved. (The term "bladder capacity" as used here denotes not the absolute volumetric capacity of the bladder, but rather the amount the child will void when it has the normal desire to do so.) The bladder capacity measurements of 30 enuretic children have confirmed previous reports[6] that the enuretic child has a much smaller than normal bladder capacity, in effect retaining the bladder capacity of a 2-year-old child, which is much too small to hold the entire output of night urine of a child aged 4½ years or older.

Primary enuresis, therefore, is due to the improper development of bladder capacity of a child through the inadequate use of its voluntary mechanism. Many children correct this at a later age, which accounts for the fact that they "outgrow" their enuresis. In a study of 4,294 children, Bloomfield and Douglas[2] showed that the 12.2% incidence of enuresis in 4½-year-old children drops to 7.3% among children aged 7¾ years. Those who continue to be enuretic during puberty and into adolescence or even adulthood, have, as our studies show, simply retained an infantile bladder capacity. Some children compensate for it by automatically reducing their fluid intake and by frequency of micturition by day and by night.

While observers have noted that enuretics have smaller bladders and increased urinary frequency, the precise reason for these conditions seemed to have escaped them. The implication was that this departure from the normal was due to some congenital anomaly or a mysterious quirk. Actually, all children start life with a small bladder which they must enlarge as they grow older. For some the transition is easy, for others quite difficult, and for still others impossible, without intelligent medical help. All children are thus potential enuretics. They can grow into enuresis as well as out of it. The critical stage for them is the period in their life between the ages of 2 and 4½ years. It is at this stage that steps to foster proper development of the bladder and to prevent enuresis must be taken. When it is realized that there are about 2 million enuretics in the United States (calculated on the basis of the 1950 census), the magnitude of the problem from the point of view of prevention becomes clear. These studies suggest that the potential enuretic can be spotted by the age of 3 years and that it may be profitable to take steps at that age to prevent the development of enuresis.

In a series of 30 enuretics it has been possible to eliminate the enuresis by enlarging their bladder capacity to a size commensurate with their age and stature. The treatment of enuresis, therefore, can be placed on a rational basis. Past efforts, which were primarily designed "to benefit the bed and not the child," are futile and should be abandoned. In this category belong such suggestions as dehydration, the strict forbidding of fluids after 4 p. m., dragging the child out of his bed at night to void, clocks to wake him, and gadgets to shock him out of his sleep once involuntary leakage of urine has occurred. Equally futile are rewards and punishments for something a child cannot control without help.

Training Program.—In our hands the bladder capacity of the enuretic could be increased by a simple program which can be carried out by children who are mature enough to cooperate and whose parents are intelligent enough to follow the training scheme.

For a few days before any therapy is starte the child, with the mother's help, is asked to kee a "voiding chart" to record the fluid intake an urinary output. The time and the amount of eac micturition should be noted by asking the child t void into a glass measuring cup which will measur at least up to 14 oz. The very fact that the chil takes an active part in his training program i beneficial psychologically, especially, when he made to understand that his bladder is as yet to small and that he will have to try to make it large to become cured of the nuisance of bedwettin The "voiding chart" will show that the child voic in amounts of 2, 4, or 6 oz. (60, 120, or 180 cc. An occasional 8-oz. (240 cc.) voiding is not goo enough to cure enuresis. The child is now instructe to force fluids during the day and to hold his urin as long as possible. This is precisely the reverse what is being practiced today. It will take an where from three to six months, depending on th initial capacity of the bladder and the cooperatio of the patient and parent, before a satisfactor bladder capacity is reached. During the trainin period, the wet bed is strictly ignored.

The use of anticholinergic drugs during the da and at bedtime is often helpful to accomplish more rapid distention of the bladder. Atropin sulfate, propantheline (Pro-Banthine) bromide, oxyphencyclimine (Daricon) hydrochloride are helpful in relaxing the detrusor and in the distentio of the bladder with its own urine so that graduall larger amounts are voided.

Sometimes it is necessary to overcorrect a smal bladder. While a 12-oz. capacity and a voidin volume of 8 to 10 oz. during the day can be sufficient to eliminate enuresis in most instances, for permanent cure it may be desirable to reach th higher capacity of 14 oz. (420 cc.). It should b emphasized that the cure of enuresis is not a simpl matter of ounces held or voided. Each child i highly individualistic and the "normal" (nonenuretic) bladder capacity of one child may be to small for the next one, for there is no such thin as a standard child. It is perhaps trite to say tha they vary tremendously in weight and height a any given age and that their water metabolisn varies as well.

Summary

The infant has an automatic bladder and empties it by means of "detrusor micturition." Within a short span of 4½ years, most children acquire an adult type of control over their bladders and are able to hold urine and to start the urinary stream, at will, at any degree of bladder filling. In the course of this development the child first acquires the cognizance of the full bladder through the maturation of the autonomic nervous system. Next, it learns to inhibit a detrusor contraction and to hold its urine through the use of the levator ani and its pubococcygeus. The third step in this progressive development is the ability and skill to manipulate the intra-abdominal pressure through the use of

the diaphragm and of the abdominal musculature. The next and most difficult step in this process is the ability to stop and start the urinary stream at any degree of bladder filling. This is carried out through the contraction of the diaphragm and of the abdominal musculature and the simultaneous relaxation of the pubococcygeus. The development of urinary control in a child, therefore, is essentially the development of the skill in creating and manipulating intra-abdominal pressure. When complete mastery of this voluntary mechanism is achieved, the child is in a position to enlarge its bladder capacity and to double this capacity by the age of 4½ years, compared with what it was at the age of 2 years. When this has occurred, the bladder is large enough to retain the total output of night urine and the child will no longer wet the bed.

Primary enuresis is due to the improper development of adult urinary control which leaves the child with a bladder capacity too small for its age and stature. Enuresis can be cured by controlling the child's urinary output during the day to enlarge and to distend its bladder. This is done by forcing fluids during the day and by teaching the child to hold the urine as long as possible. Anticholinergic drugs can be useful in the treatment of enuresis.

416 Marlborough St.

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SHORT-TERM STUDY OF CORONARY HEART DISEASE IN A NORTH DAKOTA COMMUNITY

Robert C. Painter, M.D., Lloyd S. Ralston, M.D., Grand Forks
Robert M. Fawcett, M.D., Devils Lake, N. D., William J. Zukel, M.D.
and
Robert H. Lewis, M.D., Washington, D. C.

The authors studied data on heart disease obtained between Jan. 1 and Dec. 31, 1957, from an area containing an estimated population of 100,000. This area was taken as typical, geographically and economically, of the situation usually dealt with by the general physician. There were 40 cases of angina pectoris, 45 of definite or probable coronary insufficiency, 157 of definite or probable myocardial infarction, and 49 of sudden, unattended death. Eighty-seven patients were women and 204 were men. There were 143 deaths. Of every five serious episodes of coronary heart disease three terminated in death during the given episode. The prognosis was better if the patient lived long enough to receive medical attention and still better if he survived the first 24 hours thereafter. Except for those in the category of angina pectoris, most patients had no prior known symptoms of coronary heart disease.

This report attempts to present a cross section of the clinical picture of coronary heart disease as it occurs in a general population in North Dakota. Since this epidemiologic study of coronary heart disease was based on the reports of cases by the practicing physicians in the area, one would assume that the incidence of the different manifestations of coronary heart disease presented here might be expected to be reproducible in the practice of any general physician in a similar population.

Methods and Procedures

Early in 1956, in response to the interest shown by Dr. Paul D. White and the United States Public Health Service, plans were begun for an epidemiologic study of coronary artery heart disease in North Dakota. A six-county area in the northeastern corner of the state was selected as being the most geographically and economically suitable for such

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From the Department of Medicine, Grand Forks Clinic (Drs. Painter and Ralston); the Department of Medicine, Lake Region Clinic (Dr. Fawcett); the operational research section, Heart Disease Control Program, U. S. Public Health Service (Dr. Zukel); and U. S. Public Health Service (Dr. Lewis).

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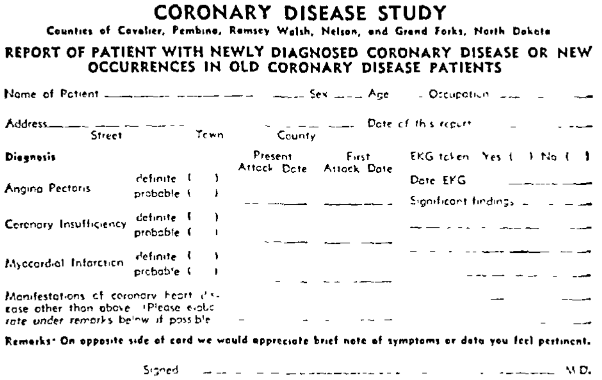
a study, the counties so selected (Cavalier, Pembina, Ramsey, Walsh, Nelson, and Grand Forks) containing an estimated population of 100,000. The physicians in this area fortunately were all members of the Grand Forks District Medical Society or, as in the case of those in Ramsey county, of the Second District Medical Society. Both of these societies expressed enthusiasm for the study and appointed three physicians, all qualified internists, to supervise the program on the local level and to work with the North Dakota State Health Department, the North Dakota Heart Association, and the United States Public Health Service. The latter appointed a medical officer to help in the collection and correlation of the necessary data.

The physicians in the area were requested to report all new manifestations of coronary disease which they encountered in their practice. To assure a uniform reporting sequence for at least one year, the reporting began Oct. 1, 1956, and was carried through Dec. 31, 1957. Only cases occurring between Jan. 1, 1957, and Dec. 31, 1957, are included in this analysis, since it was considered that reporting was most complete for this period.



CORONARY DISEASE STUDY

Counties of Cavalier, Pembina, Ramsey Walsh, Nelson, and Grand Forks, North Dakota

REPORT OF PATIENT WITH NEWLY DIAGNOSED CORONARY DISEASE OR NEW OCCURRENCES IN OLD CORONARY DISEASE PATIENTS

Name of Patient ________ Sex ___ Age ___ Occupation ________

Address ________ Street Town County ________ Date of this report ________

Diagnosis		Present Attack Date	First Attack Date	EKG taken Yes ( ) No ( )
Angina Pectoris	definite ( ) probable ( )	________	________	Date EKG ________ Significant findings ________
Coronary Insufficiency	definite ( ) probable ( )	________	________	________
Myocardial Infarction	definite ( ) probable ( )	________	________	________
Manifestations of coronary heart disease other than above (Please elaborate under remarks below if possible	________			________

Remarks: On opposite side of card we would appreciate brief note of symptoms or data you feel pertinent.

Signed ________ M.D.

Card Used for Reporting Cases of Coronary Disease.

Each case was reported by the physician on a simple reporting card (see the figure), on which it was grouped under one of several general categories such as angina pectoris, coronary insufficiency, myocardial infarction, or other manifestations of coronary heart disease. He also was encouraged to list additional data when available. Each physician was visited monthly by the medical officer, who obtained all clinical data available in all reported cases. An attempt was made to obtain a clinical description of symptoms, progress of the patient, and laboratory data. When an electrocardiogram had been made, this was obtained for photostatic reproduction by the North Dakota State Health Department. These monthly visits helped in obtaining data on some cases, the reporting of which the physician otherwise might have overlooked. In addition, all the hospitals in the area were cooperative in reporting cases of coronary disease which might have been overlooked in the busy practice of the local physician. Physicians practicing in the areas bordering the six-county area were visited every two months, and similar data were collected on any cases in residents of the six counties who might have been cared for by these physicians.

Other sources of information included morticians, coroners, registrars of vital statistics, public health nurses, and newspapers. In addition a 24-hour autopsy service was offered to the physicians in outlying areas to help in the diagnosis of deaths of unknown cause. Gross and microscopic study of this material was made in the pathology department of the medical school at the University of North Dakota in Grand Forks.

Classification of Cases

Each case was reviewed by a committee made up of the medical officer and supervising physicians, all of whom were also qualified internists. After careful perusal of clinical history, laboratory data, electrocardiogram, and progress, each case was placed in a suitable category. The diagnostic categories of coronary heart disease were as follows: angina pectoris, coronary insufficiency, myocardial infarction, and unattended deaths. Congestive heart failure, arrhythmia, and embolic phenomena also were reported if coronary heart disease conceivably provided the etiological basis.

Angina Pectoris.—The category of angina pectoris was defined as the occurrence of transitory, substernal pain with characteristic radiation to the neck, jaw, or arms, usually precipitated by some inducing factor such as effort or emotion, and amenable to prompt relief by rest or the use of nitroglycerin. Findings of physical examination and laboratory examination in these cases were normal. The electrocardiogram may have shown normal results or changes indicative of myocardial ischemia without acute change.

Coronary Insufficiency.—The category of coronary insufficiency included those cases in which the substernal chest pain was more prolonged, occurred either with effort or at rest, and was associated with acute electrocardiographic changes which might last several days or weeks. These consisted of ST-segment elevation or depression, with or without inversion of the T wave, and without presence of a Q wave. While there might have been mild fever and some elevation of white blood cell count and erythrocyte sedimentation rate (not over 20 to 30 mm. per hour), the heart sounds, lung fields, blood pressure, and pulse rate were normal.

Myocardial Infarction.—The category of myocardial infarction included those cases in which there was a more clear-cut history of sustained chest pain associated with electrocardiographic evidence of and/or a subsequent clinical course indicative of a more severe myocardial injury (fever;

elevation of white blood cell count, sedimentation rate, and transaminase level; perhaps pulse and blood pressure abnormalities; or in some instances death ensuing before such a clinical course could be established). The reviewing committee of internists interpreted all electrocardiograms, along with the clinical and laboratory data, and was the final judge as to whether a given case was classified as myocardial infarction or otherwise.

The reporting physicians were requested to report each patient as having a definite or probable case in each category. Each case was reviewed by the reviewing board, and every attempt was made to obtain sufficient criteria to place the case in a definite diagnostic category. However, in some instances, even though clinical judgment seemed to indicate a case should be in a definite category, it was necessary finally to place it in the probable diagnostic category.

Unattended Deaths.—As the study progressed, it became apparent that there was a large number of ases in which the patient died unexpectedly and without the attendance of a physician in the interal between the acute onset of his immediate anteortem symptoms and death. These deaths were rouped into the following three categories: first, nattended death due to definite coronary disease with (1) autopsy showing acute changes or (2) history of coronary disease and symptoms immediately prior to death, which were indicative of coronary disease; second, unattended death due to probable coronary disease consisting of either (1) no history of coronary disease but symptoms immediately prior to death which were suggestive of coronary disease or (2) a history of coronary disease but no known symptoms of coronary disease immediately prior to death; and third, unattended death, unknown cause, in persons with no history of coronary disease and no known symptoms of coronary disease immediately prior to death.

An attempt was made to group those cases in which angina pectoris and coronary insufficiency were secondary to other disease processes such as acute arrhythmia, anemia, congestive heart failure, and others into a separate category to be evaluated later. These cases are not included in this presentation. Likewise, in some instances the information was more suggestive of pulmonary embolism or noncoronary cardiac disease and the case therefore was eliminated.

Data

Table 1 shows all the cases collected in the study which were classified, as listed above, in the categories considered to constitute coronary heart disease. There were 291 cases in all, 70% of the patients being men. This proportion of about two men for each woman was fairly uniform in each category, except in coronary insufficiency where it was 4:1. In the six-county area the number of men and women 35 years of age and over was determined by a census to be about the same.

Fourteen per cent of the cases were listed as angina pectoris. The reviewing committee believes that this figure does not represent a true incidence of this condition in the population. These patients were ambulatory for the most part, and reliability of reporting rested entirely on the reporting physician. There was no way to check hospital records and/or death certificates and thus be able to remind the physician of a forgotten case, as was done frequently in the other categories. As a result, it is our impression that this figure is far too low.

In 17% of the total number of reported cases unattended deaths were listed; the patients died suddenly or at least before they could obtain medical attention. This, of course, represents a group of patients who ordinarily would be included neither in an analysis of coronary heart disease in a physician's practice nor in a hospital service. Rather, most of them might well be coroner's cases. Among the total of 291 subjects classified as having coronary heart disease, there were 143 (49%) "deaths." Of the latter, 49 (17% of the total number of cases) were "unattended deaths," leaving 94 deaths (32% of the total number of cases) as occurring among those patients who had myocardial infarction and received medical attention.

TABLE 1.—*Data on 291 Patients with Coronary Heart Disease*

	Diagnostic Categories,* No. of Cases								
		CI		MI		Unattended Deaths			
Patients, No	Angina Pectoris	Definite	Probable	Definite	Probable	UDD	UDP	Total Cases, No.	Deaths, No.
Male	27	32	3	79	28	10	25	204	95
Female	13	8	2	29	21	2	12	87	48
Total		40	5	108	49	12	37		
Grand total	—							—	—
No.	40	45		157		49		291	143
%	14	15		54		17		100	49

* CI: coronary insufficiency; MI: myocardial infarction; UDD: unattended death, definite coronary heart disease; UDP: unattended death, probable coronary heart disease.

In addition to the 291 cases of coronary heart disease shown in table 1, there were 51 cases (35 men and 16 women) placed in the category of "unattended deaths, unknown cause." These cases were not included in table 1, because, by definition, there was no clinical or pathological evidence to indicate that death was due to coronary heart disease, and it was believed that a clearer picture of the definite or probable coronary heart disease diagnosed in this population would be obtained by their omission. However, one cannot ignore the fact that, if postmortem examination could have been performed on all 51 of these persons, some of them certainly would have been reclassified in the group "unattended death from coronary heart disease." (A preliminary report on the men in this study who had coronary heart disease was presented at the American Public Health Association Annual Meeting, St. Louis, Oct. 30, 1958. Since these data were evaluated, 30 additional cases which are classified as "unattended death from coronary heart disease" have been collected on the basis of additional death certificate data.)

In table 2, the 157 cases of myocardial infarction are presented in regard to sex, age, and survival or death. Among those of all ages who survived the attack, men predominate in a ratio of 3:1 as compared to a ratio of 2:1 among those who died. However, if one excludes patients aged 75 years and over, there is a definite rise of the ratio of men over women to 3:1, whether surviving or not. Among those aged 75 and over who survived there are only three men and two women, while among those in this same age group who died there are almost twice as many women as men (18 and 10 respectively). The women with infarction are fairly consistently seven years older than the men in this series. If those over the age of 75 years are excluded, this difference drops to five and three years respectively. The average age of men and women who die of myocardial infarction is exactly 10 years above the average age of those who survive the attack. It is important to note, however, that there was no appreciable difference in age at death between men and women in the older age group (82 versus 80 years).

TABLE 2.—*Sex and Age Distribution in One Hundred Fifty-seven Patients with Myocardial Infarction*

	Age, Yr					
	All Ages		Under 75		75 and over	
Patients	No	Average Age	No.	Average Age	No.	Average Age
Living						
Male	47	57	44	55	3	80
Female	16	64	14	60	2	76
Total	63	...	58	..	5	...
Dead						
Male	60	67	50	64	10	82
Female	34	74	16	67	18	80
Total	94	...	66	...	28	...

The fact that 94 (60%) of 157 patients with myocardial infarction died is noteworthy. This high fatality rate would suggest that there might have been under-reporting of nonfatal cases of myocardial infarction by physicians or that persons with less severe clinical symptoms did not seek medical attention and were not all recognized. In spite of this fact, the members of the reviewing committee, who are acquainted with the practitioners and the standard of medical practice in this area, believed this to be an accurate reflection of clinically manifest coronary heart disease as seen in the private practice of physicians in this population.

Further analysis of these deaths from myocardial infarction as compared to all other deaths is presented in table 3. If we consider only those d ceased persons who obtained some medical atte tion and whose cases were thus classified myocardial infarction, it is interesting to n that 27 died within the first hour after obtaini medical attention and that a total of 56 (60% the myocardial infarction deaths) died within t first 24 hours after obtaining medical attenti However, one can obtain a different perspective surveying all the deaths in the study, that is deat presumably all secondary to coronary heart disea There were 143 such deaths, 49 (34%) being u attended deaths in persons who did not, or co not, obtain medical attention prior to death. Twe ty-seven persons died within one hour after c taining medical attention, and 105 (73% of deaths) died before or within 24 hours of obtaini medical attention.

TABLE 3.—*Deaths from Myocardial Infarction*

	Time Lapse							Unatten Death
Myocardial Infarction	Within 1 Hr. of Admission or Being Seen	1-12 Hr.	13-24 Hr.	1-7 Days	8-14 Days	Over 14 Days	Total	Type*
Definite ...	7	9	6	11	4	9	46	UDD
Probable .	20	10	4	11	1	2	48	UDP
Total† ..	27	19	10	22	5	11	94	Total

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* UDD: with definite coronary heart disease; UDP: with prob coronary heart disease.

† Total of 143 deaths occurred: 49 (34%) died before they could tain medical attention: 56 (39%) died within 24 hr. after obtai medical attention; and 105 died (73%) died before or within 24 hr. obtaining medical attention.

In table 4 the deaths have been analyzed in co parison with cases of survival. No deaths occurr among patients reported to have had angina pe toris alone. If we consider all of the patients in t study, with the exception of those given a diagno of angina pectoris, as having a serious episode coronary heart disease, and if we also exclude t 51 cases listed as "unattended death, unknow cause" for the reasons already discussed, there ar a total of 251 such cases. In this group, 45 patient with coronary insufficiency and 63 with myocardia infarction survived, i.e., a total of 108. Thus, abou three of every five cases of a serious episode o coronary heart disease terminated in death. If w consider only the patients who received medica attention, i. e., the coronary insufficiency and myo cardial infarction groups, there were 202 patient

TABLE 4.—*Survival Statistics of Patients with Serious Episodes of Coronary Heart Disease*

	Total No. of Cases	Survivals, No.	Death No.
Coronary insufficiency Myocardial infarction Unattended death, definite Unattended death, probable	251	108	143
Coronary insufficiency Myocardial infarction	202	108	94
Surviving 24 hr. after medical attention	146	108	38

lived long enough to receive medical attention 146 who were still alive at the end of the first 24 hours. Applying the figure of 108 surviving patients to these totals. It would appear that, if a patient survived a serious episode of coronary heart disease long enough to receive medical attention, he had a somewhat better than even (108 survivals s compared to 94 deaths) chance to survive that pisode. Furthermore, if he survived the first 24 ours, his chances of surviving that episode rose to bout 3:1 (108 survivals as compared to 38 deaths).

In table 5 all cases in the study are analyzed ith regard to the known occurrence of symptoms r attacks of coronary heart disease prior to the eported episode. Of the 40 patients given a diagnosis of angina pectoris in this population in 1957, 4 (85%) had experienced symptoms from one eek to seven years prior to diagnosis. Six patients 15%) had consulted a physician and had been given a diagnosis of angina pectoris on the first appearance of symptoms. In the categories of coronary insufficiency, myocardial infarction (deaths); unattended death, definite coronary heart disease; and unattended death, probable coronary heart disease, there were no known previous symptoms in 50 to 60% of all cases. However, among those patients with myocardial infarction who survived the episode, 46 (74%) had not previously experienced symptoms. The types of prior coronary heart disease experienced by patients included angina pectoris, coronary insufficiency, myocardial infarction, and congestive heart failure. Analysis of those cases that terminated in death during this episode (myocardial infarction; unattended death, definite coronary heart disease; and unattended death, probably coronary heart disease) revealed that the prior incidence of angina pectoris and myocardial infarction was identical in each category. There was a wide range in the length of time from the first symptom or attack until death ensued. In some cases this time was reported by the attending physician or the patient's family as being "many years." To establish an approximate average, it was arbitrarily decided to use 10 years to replace this term in an individual case for the purpose of estimating duration of symptoms. If this is done one finds that, among the myocardial infarction deaths, those patients who had had angina pectoris developed this symptom an average of two years before death, while those having had a prior episode of myocardial infarction first experienced the symptom an average of 5.2 years before the final episode. This difference was not present in the category "unattended death, definite coronary heart disease," and since there were only two cases of each, no real conclusion can be drawn. In the category "unattended death, coronary heart disease probable" there were eight cases of angina pectoris and eight of myocardial infarction, with a survival time of 3.2 years for each category.

Among patients surviving the reported episode (coronary insufficiency and myocardial infarction), there is a greater incidence of angina as compared to any other type of coronary heart disease existing prior to the reported episode. Thus, in the coronary insufficiency group there are 12 patients who had had angina pectoris previously as compared to 4 who had experienced previous myocardial infarctions. In contrast to this, however, the prior infarctions had occurred on the average almost six years before, as compared to a duration of two and one-half years of angina pectoris. In the myocardial infarction (living) category the frequency of prior angina pectoris as compared to infarction was less marked, and the time of prior occurrence for both was about two years.

TABLE 5.—*Prior Manifestations of Coronary Heart Disease*

		No Known Prior Symptoms		History of Prior Symptoms		Prior Symptoms or Attack		Duration of Time Between First Occurrence of Prior Symptoms and Reported Episode	
Diagnostic Category	Cases, No.	No.	%	No.	%	Type	No.	Range	Approximate Average, Yr.
gina pectoris	40	6	15	31	85	Angina pectoris	31	1 wk. to 7 yr.	1.3
onary insufficiency	45	25	56	20	44	Angina pectoris	12	1 mo. to 10 yr.	2.5
						Coronary insufficiency	4	1 mo. to 3 yr.	1.7
						Myocardial infarction	4	4 to 8 yr.	5.7
ocardial infarction (patients living)	63	46	74	17	26	Angina pectoris	9	1 mo. to 5 yr.	1.8
						Myocardial infarction	6	3 mo. to 6 yr.	2.1
						Congestive failure	2	1 yr.	1.0
ocardial infarction (patients dead)	94	55	59	39	41	Angina pectoris	13	1 mo. to many yr.	2
						Coronary insufficiency	7	6 mo. to 9 yr.	3
						Myocardial infarction	13	18 mo. to 15 yr.	5.2
						Congestive failure	6	2 mo. to many yr.	6.3
attended death, definite coronary eart disease	12	7	58	5	42	Angina pectoris	2	5 to 8 yr.	6.5
						Myocardial infarction	2	2 to 6 yr.	4.0
						Congestive failure	1	2 mo.	...
attended death, probable coronary eart disease	37	19	51	18	49	Angina pectoris	8	1 to 8 yr.	3.2
						Coronary insufficiency	1	2 yr.	...
						Myocardial infarction	8	6 mo. to 5 yr.	3.2
						Congestive failure	1	2 yr.	...

Summary

A study was made of the clinical spectrum of coronary heart disease in the population of six counties of North Dakota over a period of one year, as seen through the eyes of the practicing physicians serving that area. The clinical findings of this unique study, which was made possible through the interest and participation of all practicing physicians in the area in cooperation with public health agencies, are as follows.

Of the persons in this population who developed manifestations of coronary heart disease of sufficient severity to result in their being seen by a physician, 14% had manifestations diagnosed as angina pectoris, 15% had coronary insufficiency, 54% had myocardial infarction, and 17% died from coronary heart disease before they could receive medical attention.

When all diagnostic categories are considered as a whole, the incidence of coronary heart disease among men was twice that among women. At ages under 75 years, a ratio of 3:1 was found for the incidence of myocardial infarction among men as compared with women. However, at ages 75 years and over the ratio became two men to three women.

Men under 75 years of age with a diagnosis of myocardial infarction were, on the average, four years younger than women of the same age group in this diagnostic category. The average age of me and women in this age group who died of my cardial infarction is nine and seven years, r spectively, above the average age of those su viving the attack. However, in the patients 75 yea of age and over there is no difference between th sexes in regard to average age at death.

Sixty per cent of all patients with myocardial i farction died during the particular episode whic occurred in the course of this study.

Analysis of death and survival rates reveals th three of every five cases of a serious episode coronary heart disease terminated in death duri that episode. If the patient survived long enou to receive medical attention, his chances of survi ing that particular episode were about even. Ho ever, if he survived the first 24 hours after obtai ing medical attention, this ratio rose to 3:1 in fa of his survival.

Except for those in the category of angina pe toris, most patients had no prior known sympto or manifestations of coronary heart disease. Amo those that did, angina pectoris and myocardi infarction occurred most frequently. Among tho who died during this reported episode, angina pe toris and myocardial infarction had occurred wi equal incidence, while in those surviving the ported episode angina pectoris had previously c curred more frequently than myocardial infarcti

CLINICAL NOTES

REPORT OF A CASE OF BOTULINUS POISONING

Harold P. Sutherland, M.D., Idaho Falls, Idaho

A 41-year-old woman was first seen at 5 p. m. on July 29, 1959, about 28 hours after ingestion of four or five slices of odd-tasting prepared beets. Earlier in the day she had noted difficulty in reading the newspaper and had had some diplopia. Her husband and daughter, who had also eaten the beets, had vomiting and loose bowel movements during the day, in addition to the visual symptoms. They had difficulty in forming words, and their legs felt like wooden sticks. On examination, the woman's blood pressure was 128/64 mm. Hg, body temperature 98.2 F (36.8 C), pulse rate 72 per minute, and respiration rate 20 per minute. Findings of laboratory studies, ordered at the time of admission, were as follows: hematocrit, 40% volume of cells; hemoglobin level, 12.3 Gm. per 100 cc.; white blood cell count, 6,900 per cubic millimeter, with a differential of 67% segmented and 6% band cells, 24% lymphocytes, and 3% monocytes. Findings of urinalysis were specific gravi 1.008, pH acid, and urine negative for sugar a albumin.

A diagnosis of botulinus poisoning was made the emergency room. The patient noted that s and her family had eaten slices of odd-tasting bee at the last noon meal. Several of the children in t family had not eaten the beets, but the patie her husband, her daughter, and her father-in-la had ingested the beets and had a marked similari of symptoms. The diagnosis could not be prove at this time but was felt to be suspicious enough warrant an order for polyvalent antitoxin. The re of the jar of beets had been discarded prior to a mission, and the only specimen available for stud was a jar processed at the same time by the da gerous open-kettle method. This sample of bee showed marked spoilage, and there were some gra positive, spore-forming rods on the smear. On fu r testing, however, the material in the second jar of beets was not poisonous when injected into unprotected guinea pigs. Nevertheless, I believe that, inasmuch as there were three deaths in the two families and two other members exhibited the classic symptoms of botulinus poisoning, there is no doubt concerning the diagnosis. Polyvalent botulism antitoxin was obtained by air transport from Portland, Ore., Los Angeles, Denver, and Pearl River, N. Y.

The patient was given 1 oz. of castor oil, and administration of 1 oz. of a compound containing dihydrostreptomycin sulfate, polymyxin B sulfate, and pectin, with activated attapulgite (Claysorb) as the adsorbent agent (Polymagma, plain), was ordered after successful administration of an enema; it was believed that the Polymagma would absorb any poison remaining in the gastrointestinal tract. Chloral hydrate was given for sedation on the night of admission.

The next morning the patient suffered from extreme lassitude, weakness, and vomiting, and she continued to complain of visual symptoms. Her speech had become thicker. An infusion of 5% dextrose in isotonic sodium chloride solution, with 40 mg. of potassium chloride, was started at 7:30 a. m. The initial dose of 80,000 units of polyvalent botulism antitoxin was given on July 30, at 11 a. m. This was diluted 1:10 with 10% dextrose in water. The total 2,400-cc. volume of infusion solution was given during the next 18 hours. The antitoxin was given after the initial dose of infusion solution, at the rate of 10,000 units diluted to 300 cc. with 10% dextrose in water, every four hours for the next five and one-half days. On Aug. 4 there was improvement in the patient's speech, control of nuscles of swallowing, breathing, and vision.

Shortly after administration of the antitoxin had een started, the patient complained of increased lifficulty in swallowing and breathing and became yanotic. On July 30, at 3:30 p. m., she had comlete paralysis of the respiratory muscles and was laced in a Drinker respirator. To obtain sedation nd analgesia, she was given 50 mg. of promethazine Phenergan) hydrochloride and 75 mg. of meperiline (Demerol) hydrochloride every four hours. This losage was later decreased to 25 mg. of promethaine and 50 mg. of meperidine every four hours.

The patient was administered oxygen 4 to 6 liters er minute, first by nasal catheter and later by asal cannula. She was placed also on Levine-tube suction for the first two days.

During the second day in the respirator she developed a temperature of 102.6 F (39.2 C) and was given 3 cc. of Bicillimycin, which contains 600,000 units of benzathine penicillin G, 300,000 units of buffered crystalline penicillin, 300,000 units of procaine penicillin G, and 1 Gm. of streptomycin sulfate. Administration of this combination of antibiotics was repeated for four days.

On the third day in the respirator the patient's speech improved. Tenacious sputum was a problem, and on the fifth day in the respirator she was started on continuous administration of Tergemist, a mucolytic, detergent aerosol solution, which made the secretions less tenacious. On the seventh day in the respirator, therapy with botulism antitoxin was discontinued, as she was regaining her speech and had only minimal visual symptoms.

On Aug. 5, a roentgenogram showed increased bilateral markings in the lungs. The white blood cell count was 11,000 per cubic millimeter, with a differential count of 68% segmented cells, 4% band cells, and 28% lymphocytes. Her body temperature was 101.4 F (38.6 C) on the morning of Aug. 4 and 101 F (38.33 C) on the morning of Aug. 5. In addition to the intramuscularly given penicillin-streptomycin combination, 0.5 Gm. of oxytetracycline (Terramycin) was given intravenously.

On Aug. 7 another x-ray film supported the diagnosis of "early diffuse bronchopneumonia." Chloramphenicol, 1 Gm. intravenously and 0.5 Gm. intramuscularly, to be repeated every six hours, and oleandomycin phosphate, 0.5 Gm. intravenously, were given.

Sensitivity tests showed the incriminated organism to be a coagulase-positive staphylococcus, which was sensitive to erythromycin, chloramphenicol, kanamycin sulfate (Kantrex), oleandomycin phosphate, and ristocetin. On Aug. 9, chloramphenicol therapy was discontinued, and 150 mg. of erythromycin was given intramuscularly every four hours until Aug. 15. Oleandomycin phosphate, 1,000 mg., was given intravenously, and kanamycin sulfate, 0.5 Gm. four times daily, was given intramuscularly. Because the culture showed considerable yeast overgrowth, a suspension of nystatin, containing 400,000 units, was given every four hours by mouth. The patient was afebrile on Aug. 13; erythromycin and kanamycin sulfate therapy was discontinued on Aug. 15, but Ilosone (propionyl erythromycin ester) in capsules of 250 mg. was given four times daily.

When removed from the respirator on Aug. 8 and given oxygen by nasal tube, she developed a rash over her back. There were no other symptoms of serum sickness, but since this was a definite possibility she was given 80 units of ACTH as a prophylactic measure.

The patient was discharged to her home on Aug. 21, 1959, 23 days after admission. Her eye movements, swallowing, and general strength improved markedly during the week after discharge, but two weeks later she had severe diarrhea which necessitated hospitalization.

The patient's husband required levarterenol (Levophed) bitartrate therapy to maintain his blood pressure, and intravenously given amobarbital (Amytal) sodium and intramuscularly given phenobarbital to control convulsions. The husband, the daughter, and the husband's foster father died from botulinus poisoning. The foster father died before the respirator or antitoxin could be used. The husband had hypotension, bilateral pneumonia, and complete renal shutdown a day before his death, on the 10th hospital day. The daughter died on the third hospital day.

Summary

A 41-year-old woman was admitted to the hospital 28 hours after having eaten beets contaminated with botulism toxin. Therapy consisted o administration of 350,000 units of botulism poly valent antitoxin, eight days in the Drinker respi rator, antibiotics, and supportive measures. Thi patient recovered. A total of 1,050 cc. of hors serum was used without apparent toxic effects.

1050 Memorial Dr.

The polyvalent botulism antitoxin used in this study w furnished without charge by Lederle Laboratories, Divisic of American Cyanamid Co., Pearl River, N. Y.

CONSTANT TENSION SPRINGS ON LONG LEG BRACES TO ASSIST THE QUADRICEPS FEMORIS

Harold M. Sterling, M.D., Brighton, Mass.
and
Frederic J. Kottke, M.D., Minneapolis

Patients with weakness or paralysis of the extensors of the knee, especially when this is associated with weakness or paralysis of the hip extensors, have great difficulty standing and walking. Many devices have been designed to support the knees, ranging from simple gutter splints, plaster splints, and nonjointed bars to jointed knee braces with knee locks. Ambulation with a stiff knee is difficult for a person who has normal strength and is a great problem for a person with paresis or other disabilities. For this reason many attempts have been made to design a brace which allows flexion during sitting and flexion and support during walking. A knee joint allowing 2 to 4 degrees of extension beyond 180 degrees offers fairly good support to the patient with moderate weakness in both hip and knee when he is standing or walking, but it requires active muscular force, either in the knee extensors themselves or in the hip extensors, to extend the knee.

Where there is weakness of somewhat greater degree in both of these groups of muscles, such a brace becomes less satisfactory, and the patient often resorts to using the mechanical knee lock on the brace to obtain stability. More than 50 years ago mechanical knee extensors in the form of rubber bands or springs appeared, but they have bee of limited use[1] because the contractile force rubber bands and coil springs diminishes linear with shortening, so that at full extension of t knee (the point at which the patient would li maximum extensor force) these devices offer the least resistance to flexion. If the tension is increase at full extension, the patient becomes unable flex his knee.[2]

Prosthetic equipment research[3] has recentl turned attention to the use of constant-tensio springs[4] in many devices.[5] This report concerns th design and manufacture of long leg braces wit constant-tension knee-extension supports for pa pients who are unable to stand and walk becaus their quadriceps are too weak when the knees ar extended.

Construction

The brace itself (fig. 1) is a light double-bar lon leg brace with high and low thigh bands and high calf band. The ankle joint is prescribed t compensate for the disability of the specific ex tremity. In several of our cases a freely movin ankle joint with no stops or springs was adequate In others, posterior stops or dorsiflexor spring were necessary because of weakness of the dorsi flexors of the ankle. The knee joint is a freely mov ing nonlocking joint, allowing extension to abou 183 degrees. Both thigh bars are extended 2 to 3 in below the knee joint. A constant-tension spring i

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From the Department of Physical Medicine and Rehabilitation, University of Minnesota Medical School.

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mounted on a ball-bearing pulley at the end of each extension arm, and the end of the spring is attached to the bar of the lower leg section to provide a constant tension extending the knee joint. It is necessary to keep the extension arm of the brace as short as possible, since the projecting points will limit flexion inside a trouser leg and may damage clothing.

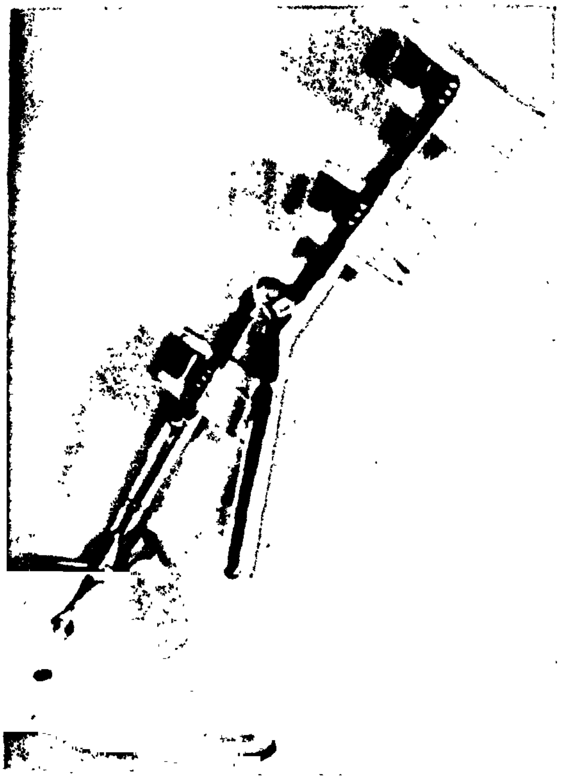

Fig. 1.—Brace before attachment of springs.

The strength of the springs to be used can be estimated easily by applying a scale or strain gauge[6] to the brace at the proposed point of attachment of the springs and noting the force necessary to extend the lower leg with its brace and shoe when the patient is seated. When the patient has some strength in his knee extensors, he should assist in this process, thus lowering the necessary spring strength. A spring which can exert one-half of the necessary force is mounted on the freely moving pulley on each of the extension arms (fig. 2). The knee joint of the brace is centered at the center of flexion of the knee but lies posterior to the line of the thigh bar and its extension arm so that the knee joint can extend slightly beyond 180 degrees.

Report of Cases

Case 1.—A 6-year-old boy with moderately severe general weakness due to amyotonia congenita was able to walk five or six steps without braces with Kenny sticks. He was fitted with lightweight long leg braces with spring-extension knee joints in December, 1957. He found that he could stand and balance immediately. Within one month he was able to walk with a 4-point gait and to walk up and down small stairs unassisted, with the braces and Kenny sticks. For the past six months he has been able to walk using sticks, but no braces, and attend public school. His gait continues to improve.

Case 2.—Another 6-year-old boy had extreme weakness of the left leg as a result of having poliomyelitis in the fall of 1957. He was originally fitted with a long leg brace with a drop lock, but he was unable to walk with the knee unlocked in spite of several months' of physical therapy and gait training. In July, 1958, he was fitted with a brace with spring knee extensors. By January, 1959, he was able to walk quite well without the brace and, at the time of this writing, walks with an almost normal gait without the brace or sticks.

Case 3.—A 60-year-old man with weakness due to compression of the spinal cord at L-3 and L-4, with weak hip extensors, no quadriceps action on the right, and fairly good action on the left, was fitted with two long leg braces with knee extensors in November, 1957, and was able to walk 60 ft. using a 4-point gait in December. Because he has not become stronger, he has continued to use the braces but can walk without assistance.

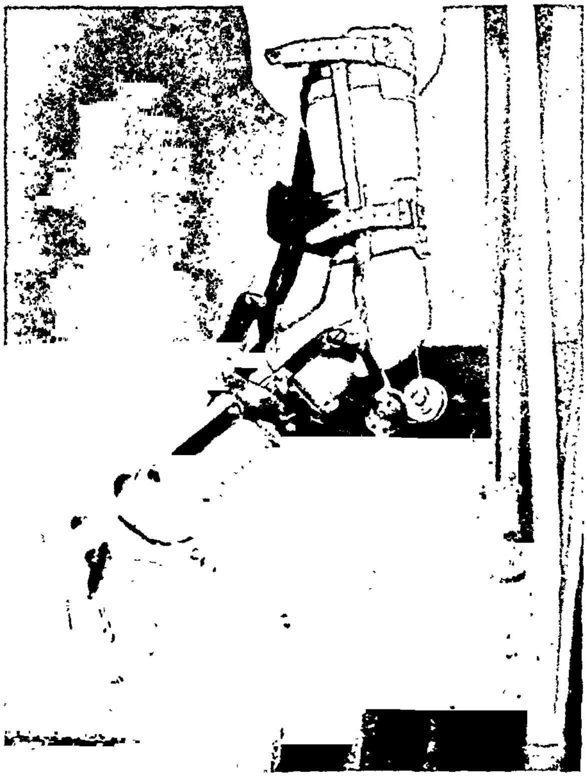

Fig. 2.—Brace completed.

Case 4.—A 3-year-old child with nonprogressive muscular atrophy which caused general weakness, most marked in the hip and knee, was unable to stand or walk without support. He was able to walk 100 ft. with gutter splints[7] and Kenny sticks.[8] In May, 1958, he was fitted with two long leg braces with knee extensors. He was able to walk with knee flexion and extension almost immediately after the braces were applied and now walks without assistance, using Kenny sticks for a swing-to and a 4-point gait.[9]

Two other patients have been fitted with similar braces too recently for a progress report.

Summary and Conclusions

A brace with constant tension throughout the range of knee motion has been described. Proper tension allows the quadriceps to participate in walking where residual strength is present, and thus the muscle can become stronger through use. Patients require less hip-hiking (elevating the pelvis on the affected side as the leg is swung forward) for walking and walk with a more normal gait. The freely flexed or extended knee joint offers greater ease in sitting and standing. In two patients, ambulation with braces developed quite rapidly and the braces were soon discarded, although both had had unsuccessful gait training directed at independent ambulation previously. Two continue to use these braces because of pe weakness.

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ANAPHYLAXIS.—In the course of about a 5-month period, I had several episodes of folliculitis of one or the other nostril, and each of these episodes responded nicely to oral penicillin and bacitracin ointment topically. The day of this occurrence, another such episode had begun in the early afternoon. Bacitracin was used right away, but the soreness was increasing and when I got to my quarters, I took 4 oral penicillin tablets (800,000 u). At about 2130 hours, I took 4 more, the last of my supply. . . . I decided to go to the hospital and take penicillin intramuscularly, thus eliminating the need to awaken for oral medication. 600,000 units of procaine penicillin were administered at approximately 2235 hours. In past years, some 8 to 12 such injections had been received, none of which caused an allergic reaction. . . . Returning to my quarters I prepared for bed. While in the bedroom, about 2300 hours, moderate tenesmus was experienced. This was followed rapidly by a violent pounding sensation at the top of my head and . . . by a sensation of extremely heavy radial pulsations. Added to these symptoms was the sensation of a generalized erythema. Although these symptoms appeared successively, I doubt that the total elapsed time was more than 1½ minutes. It was probably at this point that I realized what was taking place, and told my wife to call the hospital O. D. and tell him I was having anaphylaxis and to please hurry. I lay down on the bed, vomited suddenly and uncontrollably about three times, and for the next few minutes the account can no longer be one of personal observation. There is no recollection of dashing to the bathroom, which I am told I did, and which is where I was when the medical officer arrived. . . . His case report: . . . "Patient was pulseless and unresponsive. Apex beat 50-60 per minute. 05 cc. of adrenalin was administered subcutaneously and response began in a few minutes. A second injection was given 5 minutes later." I regained consciousness. . . . Recovery was rapid after this and the adrenalin side-effects gradually subsided.—Lieut. Col. Martin Putnoi, MC, U. S. Army, Anaphylaxis—A Personal Experience, *Military Medicine,* June, 1959.

COUNCIL ON DRUGS

Report to the Council

The Council has authorized publication of the following report.

H. D. Kautz, M.D., *Secretary.*

This report, prepared by the Subcommittee on Breast and Genital Cancer, is the result of a 12-year collaborative undertaking to study the effect of androgen and estrogen therapy in the treatment of disseminated mammary cancer. As one of the earliest projects of this type, it has served to blaze a trail for a number of studies which have followed. It will undoubtedly serve as a base line for comparative evaluation of studies which are under way in the field of cancer. A great deal could be said about the devotion of the two men who originally headed the project and who have since died, namely, Drs. Ira T. Nathanson and Earl T. Engle. The enthusiasm and effort of the collaborators and the members of the subcommittee speak well for the participants. Credit should be given to those firms in the pharmaceutical industry which cooperated and so generously provided the products used by the investigators. The present members of the Subcommittee on Breast and Genital Cancer, headed by Dr. Ian Macdonald, are to be congratulated on their integrity and resolution in assuming the responsibility for the follow-up and reanalysis and in discharging their duties to the medical profession by assembling and interpreting the data from which this report is derived. Copies of the data and statistics used in preparing this report ("Accumulated Statistology") are available on request from the Secretary, Committee on Research.

Norman De Nosaquo, M.D.,
Secretary,
Committee on Research.

ANDROGENS AND ESTROGENS IN THE TREATMENT OF DISSEMINATED MAMMARY CARCINOMA

RETROSPECTIVE STUDY OF NINE HUNDRED FORTY-FOUR PATIENTS

In the fall of 1947, the Therapeutic Trials Committee (later designated the Committee on Research) of the American Medical Association undertook the sponsorship of a co-operative investigation of the effects of steroid hormones in the treatment of advanced or disseminated carcinoma of the breast. This investigation was co-ordinated by a Subcommittee on Steroids in Cancer including Drs. Ira T. Nathanson (deceased), Frank E. Adair, Willard M. Allen, and Earl T. Engle (deceased). In 1956, the subcommittee was reconstituted and redesignated the Subcommittee on Breast and Genital Cancer. Members of the Subcommittee on Breast and Genital Cancer of the Committee on Research are Drs. Ian Macdonald (Chairman), Los Angeles; Alfred Gellhorn, New York; B. J. Kennedy, Minneapolis; and Samuel G. Taylor, III, Chicago. With the support of the Committee on Research, and especially of its chairman, Dr. Stuart Mudd, the subcommittee has brought to completion the study which started a decade ago. The material consists of pooled data contributed by the following 60 collaborating investigators, without whose original and continued co-operation this report would not have been possible: Drs. Paul D. Abramson, Frank E. Adair, T. J. Anglem, Lionel S. Auster, H. C. Ballon, R. W. Begg, Frederick Hardy Bowen, A. J. S. Bryant, William Y. Burton, Franz Buschke, L. R. Chauncey, R. L. Clark, William A. Cooper, A. R. Curreri, Charles Eckert, Lucille Ellison, George C. Escher, Louis A. Eshman, Barry Friedman, L. H. Garland, Leonard B. Goldman, L. W. Gorham, Robert C. Grauer, Robert B. Greenblatt, Charles B. Hanna, Margaret Hardie, Joseph A. Hepp, Roy Hertz, Robert Huseby, B. J. Kennedy, Morton Kligerman, Edwin A. Lawrence (deceased), George Q. Lee, Henry Lemon, Edward F. Lewison, Champ Lyons, Ian Macdonald, S. S. Marchbanks, E. Perry McCullagh, Barton McSwain, John M. Modlin, Paul J. Murison, Ira T. Nathanson, H. E. Nieburgs, Kenneth B. Olson, Robert J. Parsons, Karl E. Paschkis, R. W. Postlethwait, Rieva Rosh, W. C. Sealy, Reginald A. Shipley, Joseph Silverstein, Arthur G. Siwinski, James A. Stapleton, Augustus Street, Samuel G. Taylor, III, G. M. Tice, Keene M. Wallace, Grant E. Ward, and Benjamin

B. Wells. The consultants in radiology included Drs. L. H. Garland and Leo G. Rigler. The consultants in pathology were Drs. Lauren V. Ackerman, Fred Stewart, and Arthur Purdy Stout. Dr. Stanley C. Harris served as consultant in biometrics.

At intervals, usually every two years, a conference of the collaborating investigators was held at the headquarters of the A. M. A. in Chicago. At the 1956 conference, the subcommittee determined the necessity of a complete reanalysis and recoding of the information which had been contributed concerning 1,983 patients. The successful completion of this laborious project was facilitated by Dr. Alex Sahagian-Edwards, College of Physicians and Surgeons, Columbia University and Francis Delafield Hospital, New York City, who served as Research Associate to the subcommittee for a 15-month period, 1956 to 1958.

Objectives of Study

TABLE 1.—*Cases Submitted for Analysis*

Cases complying with criteria for inclusion in study:		
Androgen-treated	580	
Estrogen-treated	361	
Total accepted for study		944
Cases not complying with criteria for inclusion in study:		
Not mammary cancer	19	
Male breast cancer	2	
Information lacking	372	
Not disseminated disease	309	
Radiation-treated	105	
Castrations	69	
Combined treatment	25	
Not sex steroids	22	
Ancillary treatments	14	
Inadequate dosage	101	
Miscellaneous	1	
Total rejected from study		1,039
Total submitted for analysis		1,983

The original objectives of this investigation, as established by the parent subcommittee, were outlined at the First Conference on Steroid Hormones and Mammary Cancer in Chicago, April 4-7, 1949.[1] It soon became apparent in a study of this magnitude that certain objectives could not be achieved practically or accurately. Specifically, some of the objectives were to establish which morphologic types of breast cancer were affected by androgen and estrogen therapy, the dosage necessary to achieve favorable effects, the duration of palliation, and the criteria by which improvement could be judged. Arrangements were made with the Armed Forces Institute of Pathology for a central registry, through which surgical and autopsy specimens could be reviewed by a group of consultants. Histological changes in responsive cases were comparable to the effects of irradiation, in both epithelial and stromal elements. No histological criteria for recognition of responsive tumors were apparent, nor did these studies provide any explanation of the mechanism of hormonal action.[2] Serial roentgenograms submitted to the consultants i radiology were impossible to evaluate, due to variations in techniques. Effort directed toward th elucidation of hormonal action was considered impractical in a group study. Such *areas as th* metabolic aspects of hormonal therapy, cytochemical effects, and the morphologic and *functiona* changes induced in various tissues were not investigated.

It was the current subcommittee's *opinion* tha the data available were sufficient to allow the following analyses: (1) determination of the objectiv responses of the neoplasm to estrogenic and androgenic hormones when administered to women wit disseminated mammary carcinoma, (2) compariso of the effectiveness of androgens and estrogen (3) clarification of the criteria for selection of patients and indications for hormonal treatment b estrogens and androgens, and (4) elaboration o certain aspects of the natural history of the diseas

Methods and Materials

Reports of 1,983 patients with mammary carcinoma treated by steroidal hormones were submitte to the subcommittee by the 60 investigators. Thi report is concerned with 944 cases (table 1) whic fulfilled the following criteria: 1. The diagnosis o mammary carcinoma was established histologicall in every patient. 2. Unequivocal evidence of distan dissemination of the disease was present, which wa unsuitable for radiotherapy or surgical palliation Specifically, it was required that spread beyond th regional (axillary) nodes be demonstrable in multiple foci, or be of such extent in dominant area that irradiation was impractical, or both. Each patient represented genuine, distant dissemination s advanced as to require a systemic approach i treatment. 3. The patient must not have bee irradiated or castrated within the six-month perio immediately preceding hormone therapy. This di not exclude patients with multiple lesions who received x-ray therapy to a single symptomatic area unless such irradiation resulted in any possibilit of ovarian exposure, e. g., treatment to lumba spine and pelvis. 4. No more than one hormone wa administered during a single period of observation. 5. The hormone was administered for at least one month. 6. The patient received hormones designated by the subcommittee, with dosages in reasonable accordance with established protocols. 7. A completed initial case report was submitted and was followed by progress reports at suitable intervals.

The material consisted of an initial case report of the patient, with historical data concerning (1) diagnosis and treatment of the primary disease, (2) menstrual history, (3) past illnesses and operations, (4) treatment of metastases prior to admission to this study, (5) description of size and location of lesions as indicated on appropriate diagrams, and

(6) specification of compound and dosage schedule to be employed. The progress reports provided the following information: (1) total dose of hormone, (2) duration of therapy, (3) reason for interruption or discontinuance of therapy, (4) general condition of patient, (5) objective changes observed in each lesion, (6) side-effects and other observations relevant to hormone therapy, and (7) date of death.

TABLE 2.—*Androgen Series**

Patients, No.	Substance		Schedule of Dosage: Amount, Mg.	Schedule of Dosage: Frequency	Route of Administration
415	Testosterone propionate	A	25	3 times weekly	Intramuscular
		B	50	3 times weekly	Intramuscular
		C	100	3 times weekly	Intramuscular
		D	200	3 times weekly	Intramuscular
12	Testosterone cyclopentylpropionate		200	3 times weekly	Intramuscular
45	Stanolone		100	3 times weekly	Intramuscular
20	Methandriol		100	3 times weekly	Intramuscular
88	Methyltestosterone	A	100	Daily	Oral
		B	200	Daily	Oral
580					

* Standard of reference was testosterone propionate, 100 mg., 3 times weekly. Recommended dose of other agents in terms of estimated androgenic equivalents, as determined by an advisory panel.

Despite the attempt to centralize pathological and roentgenographic interpretations, it was impractical to interpret these data. Therefore, the interpretation of the investigator and his own radiologist or pathologist was accepted as evidence for or against tumor regression.

In the evaluation of effectiveness of hormone treatment, only evidence of objective improvement was accepted as constituting reasonably satisfactory proof of a tumor-suppressive action. The definition of objective regression, which was rigidly adhered to in the following analysis, was stated as follows: a distinct, measurable decrease in one or more dominant metastatic areas by clinical or radiographic examination, without progression of any other metastatic lesions and with no new foci of disease having appeared. Indications of subjective improvement were ignored in this study of objective data; gain in weight, relief of pain, increase in feeling of well-being, improved blood chemistries, and improvement of hematopoiesis were not regarded as objective criteria. Patients classified as exhibiting "progression" included not only those with evidence of an increased extent in any lesion or lesions while under treatment but also those in whom the disease apparently remained stationary under therapy. The static cases numbered only 29.

The primary data concerning response and survival are based on the initial treatment of 944 patients. Calculations on survival were limited to patients treated by a single sex hormone, excluding those patients who subsequently received other steroid substances or who were subjected to endocrine ablative procedures. Two hundred eight patients subsequently received one or more courses of the same or another hormone. The response to these treatments is considered separately.

Androgen Series.—A total of 580 patients received androgen therapy as outlined in table 2. Although the majority of patients were treated in accordance with the dosage schedules outlined in this table, necessary variations in the individual management of patients not infrequently required changes from one schedule to another or, less often, some departure from the recommended protocol. For this reason, the criterion of adequate dosage is based in terms of total dosage. All patients in this group were treated for a minimum period of one month, according to one of the dosage schedules shown in table 2.

Estrogen Series.—A total of 364 patients were treated with estrogenic steroids as shown in table 3, for a minimum period of one month.

Follow-up: The clinical course of 844 patients (89.4%) was followed from the beginning of steroid treatment until time of death or the time of analysis. Of the 580 androgen-treated patients, 516 (89.0%) were followed to time of death or were still alive at the time of analysis; of the 364 estrogen-treated patients, 328 (90.1%) were followed to time of death or were still alive at the time of analysis.

Results

Androgen Series.—The frequency of tumor regression among the 580 androgen-treated patients was 21.4%. The distribution of these patients by age at the time of starting hormone therapy is shown in figure 1. Due to the recommendation of the subcommittee that estrogens be avoided in the treatment of premenopausal women, the prevalence of younger women among those receiving androgen treatment is conspicuous. There were 160 premenopausal patients in this group, of whom 32 (20.0%) manifested objective regression. Objective regression was recorded for 92 (21.9%) of the 420 postmenopausal, androgen-treated patients. Within

TABLE 3.—*Estrogen Series**

Patients, No.	Substance	Schedule of Dosage: Amount, Mg.	Schedule of Dosage: Frequency	Route of Administration
155	Diethylstilbestrol	15	Daily	Oral
62	Ethinyl estradiol	3	Daily	Oral
57	Chlorotrianisene	24	Daily	Oral
29	Conjugated estrogenic substances	30	Daily	Oral
25	Dienestrol	15	Daily	Oral
21	Diethylstilbestrol dimethyl ether	30	Daily	Oral
15	Estradiol dipropionate	5	2 times weekly	Intramuscular
364				

* Standard of reference is diethylstilbestrol, 15 mg. daily. Recommended dose of other agents in terms of estimated estrogenic equivalents, as determined by an advisory panel.

the postclimacteric group, menopause occurred naturally in 277, was induced in 104, and was of undetermined nature in 39 patients. (All reference to patients being premenopausal or postmenopausal indicates their status at the start of hormonal therapy. The term "induced menopause" refers to patients who had oophorectomy or castration by irradiation prior to the beginning of hormone therapy, whether related or unrelated to treatment of the primary carcinoma.)

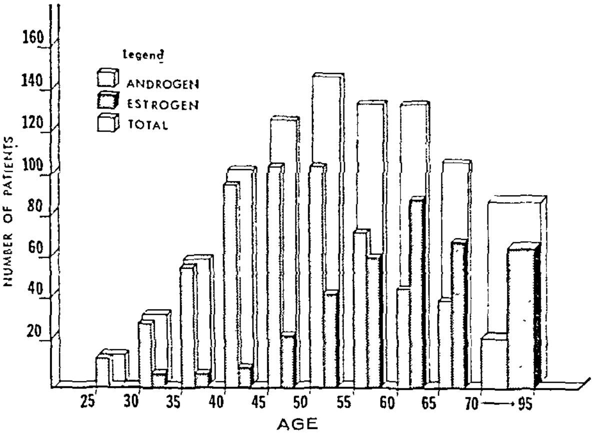

Fig. 1.—Distribution of patients by age at treatment of metastases.

The incidence of tumor regression was correlated with *treatment beginning during successive 4-year* intervals after the menopause through 16 years, and for those 17 or more years postmenopausal (table 4, fig. 2). The numerically largest group treated by androgens was in the immediate postmenopausal period of zero through four years. It is evident that nine or more years after the menopause there is an increased probability of obtaining an improvement with androgenic therapy ($\chi^2=6.65$, $p<0.01$).

Table 4.—*Incidence of Regressions Correlated with Interval Between Menopause and Beginning Hormone Therapy*

Interval Between Menopause and Hormone Therapy, Yr.	Patients, No.	Androgen: Patients Treated, No.	Androgen: Regressions: Patients, No.	Androgen: Regressions: %	Estrogen: Patients Treated, No.	Estrogen: Regressions: Patients, No.	Estrogen: Regressions: %	p*	χ^2
0- 4†	186	154	27	17.5	32	4	12.5	>0.1	0.189
5- 8	103	61	8	13.1	42	16	38.0	<0.01	7.356
9-12	125	68	18	26.5	57	21	36.8	>0.1	1.112
13-16	92	38	9	23.7	54	22	40.7	>0.1	2.191
17+	185	60	19	31.7	125	46	36.8	>0.1	0.271
Premenopausal	167	160	32	20.0	7	...	...	...	...
Unknown	86	39	11	28.2	47	25	53.2	<0.05	4.489
Total	944	580	124	...	364	134	...	...	...

* As applied here, "p" means the probability that differences between percentage regression with androgens and estrogens are due to coincidence.
† Each time interval is inclusive, e. g., from 0 through the entire 4th year = 0-4 yr.

This correlation of regression frequency with increasing postmenopausal interval is confirmed by a significant ($p<0.01$) "r_pb." (Whenever applicable, statistical methods have been used as an aid in the interpretation of results. Statistical significance is expressed in terms of probabilities that observed differences are due to chance. The smaller the "p" values, the less likely that observed differences may be attributed to coincidence. Thus, $p<0.05$ means that less than 5 times in 100 would a difference be attributed to chance; $p<0.01$ is less than 1 in 100. Conventionally, the rigid minimum requirement for significance is $p<0.01$, though a less critical but acceptable level of confidence is $p<0.05$. For those interested, statistical procedures [and their symbols] which have been applied to the data in this study are: "r," correlation of quantitative data; "r_pb" (point biserial), correlation of dichotomous values with quantitative values; "t" ratios, comparison of quantitative values; chi square, comparison of qualitative values. In every instance of chi square application, the correction for continuity has been included.)

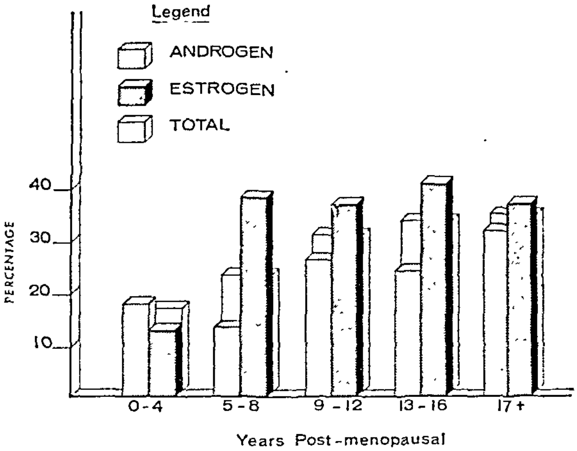

Fig. 2.—Frequency of regression by interval from menopause to treatment of metastases, shown as percentage within each 4-year group.

An evaluation of frequency of regression according to anatomic sites was attempted. Comparison of the effectiveness of androgens on metastatic involvement in peripheral soft tissue, viscera, and bone for all cases showed no significant differences (table 5). An evaluation of effectiveness on involvement of multiple system (e. g., viscera and bone, soft tissue and bone) was not practicable.

The average duration of life for all 427 patients receiving androgens as the only form of steroid therapy, and followed to time of death, was 11.4±9.9 months from institution of treatment. This period of average longevity was 19.1±12.2 months for those patients who demonstrated regressions and only 9.7±8.4 months in the nonresponsive patients ($t=8.14$, $p<0.01$). The average duration of survival of groups divided by menopausal status, primary treatment status, and responsiveness are presented in table 6. Longer survival associated with regressions is again demonstrated.

TABLE 5.—*Correlation of Incidence of Regression and Location of Metastases*

		Androgen			Estrogen		
		Patients,	Regression		Patients,	Regression	
Menopause Status	Site*	No.	No.	%	No.	No.	%
All cases	Soft tissue	69	16	23.2	98	37	37.8
	Viscera	35	10	28.6	35	14	40.0
	Bone	162	34	21.1	33	9	27.3
Postmenopausal (natural)	Soft tissue	33	6	18.2	81	33	40.7
	Viscera	10	3	30.0	25	8	32.0
	Bone	80	25	31.3	23	7	30.4
Premenopausal	Soft tissue	21	4	10.0	...	...	...
	Viscera	17	5	29.4	...	...	...
	Bone	39	7	17.9	...	...	...

* Dissemination limited to these sites; cases with involvement of multiple systems excluded.

When the androgen-treated, naturally postmenopausal patients were grouped into responsive and nonresponsive groups, and the percentage of the sample still alive at selected intervals after beginning hormone therapy was graphed (fig. 3), a significantly greater ($p<0.001$) proportion of responders was found to be alive for periods up to 48 months.

TABLE 6.—*Comparison of Average Duration of Survival of Responders and Nonresponders*

			Regression		Nonregression		
Treatment	Ovarian Status	Status of Primary Lesion	Patients, No.	Average Survival, Mo.*	Patients, No.	Average Survival, Mo.	p
Androgens	Premenopausal	Untreated	5	24	18	7	<0.001
		Treated	15	17	82	11	<0.07
		Av.	...	18	...	11	...
Androgens	Postmenopausal (natural)	Untreated	8	16	31	9	<0.05
		Treated	32	21	123	10	<0.001
		Av.	...	20	...	10	...
Estrogens	Postmenopausal (natural)	Untreated	26	20	40	8	<0.001
		Treated	15	31	87	12	<0.001
		Av.	...	27	...	11	...

* After start of hormone therapy.

Estrogen Series.—The frequency of regressions among 364 patients treated by various estrogens was 36.8%. This calculation included seven premenopausal patients, in all of whom progression of the neoplastic lesion was noted. Figure 1 demonstrates that the group treated with estrogens was comprised of chronologically older women (average age, 63 years) than the androgen-treated group (average age, 51 years).

Menopause occurred naturally in 294 cases, was induced in 16, and of undetermined type in 47. The menopause of 236 of 310 patients (table 7) occurred nine or more years before institution of estrogen therapy for metastatic disease. The regression rate of this group (37.7%) was not significantly higher than that of the group with recurrence at an earlier postmenopausal phase (27.0%). However, when the group was made more homogeneous by excluding patients whose primary lesions were untreated, or had occurred premenopausally, the r_pb is significant ($p<0.05$), indicating an increase in rate of regression as the time between institution of hormonal treatment and the menopause became longer.

The average duration of life for all 243 cases receiving estrogens as the initial and only form of steroid therapy was 16.5±16.1 months from institution of therapy (table 8). This period of average longevity was 27.3±18.2 months for those who manifested regressions and only 10.4±10.8 months for the unresponsive patients ($t=9.08$, $p<0.001$). Table 6 presents, for those women who had a natural menopause, the average months of survival after beginning hormone therapy, according to their response to treatment. Again it is obvious that patients in whom the disease regressed had a significantly longer period of survival than did those who failed to improve. In a survival curve (fig. 3), the proportion of patients alive in each period through 48 months after beginning hormone therapy was very significantly greater ($p<0.001$) for responders than for nonresponders.

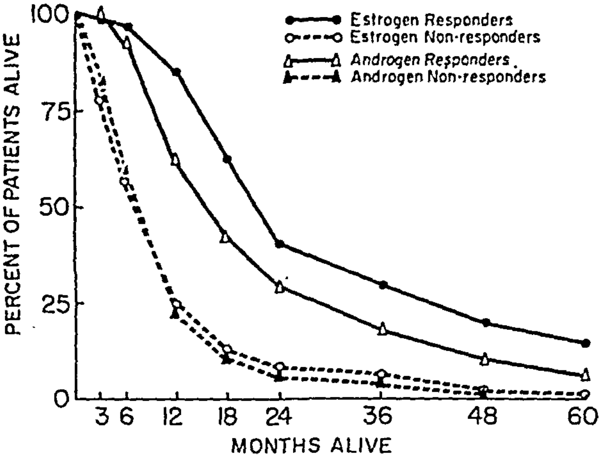

Fig. 3.—Comparative survival curves of natural postmenopausal patients from initial treatment of metastases.

Comparison of Androgen and Estrogen Series

The number of patients involved in this investigation would seem to provide an opportunity for comparing the efficacy of estrogenic and androgenic hormones in groups homogeneous with respect to the incidence of regression, response of specific disease sites, physiological and chronological age, and duration of survival. However, such effort was unrewarding in many applications of this technique because samples became too small.

TABLE 7.—*Comparison of Incidence of Regression in Terms of Ovarian Status*

		Androgen			Estrogen				
			Regressions			Regressions			
Ovarian Status	Patients, No.	Patients Treated, No.	Patients, No.	%	Patients Treated, No.	Patients, No.	%	p	χ^2
Premenopausal	167	160	32	20.0	7	0	0	...	...
Postmenopausal									
0 through 8 yr.*	289	215	35	16.3	74	20	27.0	<0.06	3.46
9 or more yr.*	402	166	46	27.7	236	89	37.7	<0.05	3.93
Unknown interval	86	39	11	28.2	47	25	53.2	...	...

* Since last menses.

Because there is a significantly different distribution of ages in the androgen-treated and estrogen-treated groups (fig. 1), comparison of therapeutic effectiveness between the entire groups might be misleading. Nevertheless, when the frequency of regression after administration of androgen and after administration of estrogen was compared in groups of the same age (fig. 4), there was a higher frequency of response to estrogens in every decade. Statistically, the differences were significant only among patients who were over 70 years of age when hormone therapy was begun.

The older the patient was at the time steroid treatment was started the more likely was a regression to occur. In the androgen-treated cases, r_{pb} revealed a correlation with less than a 5% chance of being coincidental, whereas, within the estrogen-treated group, this correlation was much stronger, $p<0.0005$. Taken collectively, $p<0.005$ indicates that age of the patient at the beginning of treatment is an important factor in responsiveness.

As indicated in figure 2 and table 4, regressions occurred more often after estrogen therapy than after androgen therapy in groups which were comparably postmenopausal. When the postmenopausal interval was arbitrarily divided into less than nine years and nine or more years, the advantage of estrogens over androgens was of modest statistical significance (table 7). Vertical comparisons in table 7 are not without some interest. However, the only such comparison which is statistically significant is in the androgen series among those patients less than nine years postmenopausal and those more than nine years postmenopausal (x^2=6.65, $p<0.01$) The point biserial correlation of regression to post menopausal interval was calculated within the mor homogeneous population, achieved by using onl patients whose menopause had occurred spontaneously and whose primary lesions had been treate postmenopausally. This correlation was statisticall significant among the estrogen-treated ($p<0.05$ not significant among the androgen-treated, an significant when androgen-treated and estroge treated patients were pooled ($p<0.01$).

TABLE 8.—*Average Survival of Patients According to Treatment*

	Androgen		Estrogen			
Status of Patients	Patients, No.	Av., Mo.	Patients, No.	Av., Mo.	t	p
All patients	423	11.4	243	16.5	5.054	<0.001
No regression	345	9.7	156	10.4	0.784	...
Regression	78	19.1	87	27.3	3.345	<0.005

So few premenopausal patients (seven) we treated with estrogens that comparisons with andr gens within this limitation were not feasible.

The incidence of regression by androgen an estrogen treatment and by site of metastases compared in table 5. In comparing the largest, mo homogeneous sample available (natural postmen pausal), it is apparent that there was no differen in the incidence of regressions in patients wit visceral or osseous lesions. In patients with so tissue lesions (lymph nodes, skin nodules, an breast), regressions occurred significantly ($p<0.0$ more often after estrogen treatment (40.7%) tha after androgen therapy (18.2%).

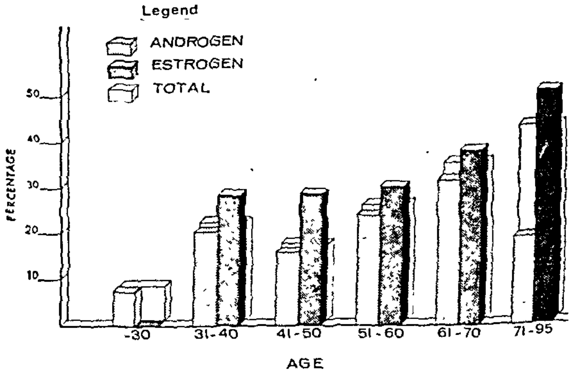

Fig. 4.—Frequency of regression by age of patient a treatment of metastases, shown as percentage within eac 10-year interval.

The excellent follow-up to time of death of thi large series provided an opportunity to compar the effect of androgen and estrogen therapy o duration of survival. The most physiologicall homogeneous sample available for this purpose wa composed of those whose menopause had occurred spontaneously (table 6, fig. 3). Fortunately, the samples were almost equal in size, 194 having been treated by androgens and 198 by estrogens. Of the combined total of 392, 111 (28.2%) were responders, and 281 (71.8%) were unresponsive to hormonal treatment. Despite the type of hormone employed, longevity in the nonresponders was virtually identical, or an average of 10 and 11 months (after beginning hormonal therapy) for patients receiving androgens and estrogens respectively. Such uniformity in lethal end-point, unrelated to treatment, is evidence of a comparable tumor-host relationship at the beginning of treatment and a further indication of the homogeneity of the sample under analysis. In table 6 it may be seen further that, among patients enjoying regression, the estrogen-treated patients survived significantly longer, on the average, than did the androgen-treated patients, or 27 and 20 months respectively ($p<0.05$).

The advantage of estrogen treatment on survival may be seen also in figure 3. Statistically, more estrogen-treated patients are still alive 6 months ($\chi^2=7.49$, $p<0.01$) and 12 months ($\chi^2=4.40$, $p<0.05$) after beginning treatment.

Repeated Courses of Hormone Therapy

One or more courses of the same, or another, hormone were used for 208 patients not included in the calculations of survival just described. Evaluation became more difficult as multiple courses of treatment constituted added variables and made comparisons more complex; a much larger sample than was available would be required for comparisons of any significance. It was apparent that, after an initial regression and subsequent reactivation, a second interval of objective regression might be obtained with hormones of the same or the opposite type. In fact, repeated regressions were obtained in some patients. Also worthy of mention was the observation of renewed remission, in occasional patients, after withdrawal of the hormonal substance which had induced the initial period of regression. Such examples of a "therapeutic" effect by omission of therapy are unusual, and the duration of the favorable response ordinarily is brief.

Comment

Validity of Study.—Certain aspects of this retrospective, co-operative study and the methods used in analyzing the available data deserve some comment. It is unfortunate that over one-half of the case records submitted were unacceptable. Contributing factors included too many investigators submitting too few cases, inadequate resources for ideal liaison with contributors and for prompt correction of deficiencies and collection of follow-up information, and failure to achieve a more effective experimental design during the planning stage over 10 years ago. Of practical importance are those exclusions suspect of producing a selective effect or making the sample for analysis biased. The exclusion of 101 cases because of inadequate dosage is justified by three items of evidence: 1. The frequency with which androgens and estrogens were used in the rejected cases was about the same as in the accepted cases. 2. Previous reports of the subcommittee have provided evidence indicating that the potential effectiveness of the sex steroids on the neoplasm is related directly to their virilizing or feminizing titer, and that regression of disease does not occur to any significant degree until clinical evidence of the physiological effect of androgens or estrogens is apparent. The minimal requirements of dose and of duration of treatment for this study are both well below the levels required for virilizing or feminizing effects and must be regarded as almost equally inadequate in antitumoral effect. 3. Another objection might be that the rejection process resulted in the acceptance of cases treated by androgens and estrogens which are not as representative as an unselected group would be, resulting in a comparison of atypical groups. The present report demonstrates conclusively that the patients treated by androgens and estrogens were comparable groups; among those who were unresponsive to treatment, average survival time was virtually identical in each series (table 6, fig. 3).

TABLE 9.—*Regression Rates According to Total Dose*

	Testosterone Propionate	
Ovarian Status	<3 Gm.	>3 Gm.
Premenopausal, %	8.8	21.5
Postmenopausal (natural), %	12.5	30.1

The criterion of a minimum period of one month of treatment was exceedingly lenient. For androgens, one month of schedule C, testosterone propionate, most commonly used, produced a dose of 1.3 Gm.; schedule A, least often used, was at the rate of only 325 mg. per month. The relative inadequacy of these dosage levels was obvious when regression rates were calculated with reference to a total dose of known effectiveness, or 3.0 Gm. in two major groups (table 9). With estrogens, a total dose of 1.0 Gm. of diethylstilbestrol is an effective level, as the following rates of regression, in naturally postmenopausal patients, will demonstrate: <1.0 Gm., 26.3%; >1.0 Gm., 47.3%. The minimum criterion of one month of treatment, at the recommended rate of 15 mg. of the substance daily, amounts to less than 500 mg., but even this is frequently an overestimate because of the number of patients with an initial intolerance and the necessity of graduated dosage at the beginning of treatment.

The duration of treatment is as important as, or perhaps of greater significance than, the total dosage. The situation just indicated for the orally administered estrogens is pertinent; some of the accepted cases were women who did not reach the minimum total dose until two or even three months had elapsed, because of difficulty in developing tolerance. A few never reached the recommended daily dose. Yet the length of treatment was an important consideration. If a total of 3 Gm. was ingested, a three-month period was required before full effectiveness of estrogens was approached, though not entirely realized for soft tissue metastasis, whereas skeletal deposits frequently required even longer intervals before objective changes of regression were demonstrable. With androgens, it seems probable that remissions were about twice as frequent in those treated for more than three months than in patients whose therapy was of briefer duration.

With such minimum criteria of dosage and duration of treatment established, it is obvious that the lenient requirements for admission to this study had a dual effect: (1) inclusion of patients in whom a favorable response may have been triggered by hormonal influences of minute dimensions, and (2) admission of potential responders in whom more prolonged treatment at recommended dosage would have achieved measurable palliation. As the latter group exceeded the former by a large margin, the process of selection was such as to diminish, rather than enhance, the true dimensions of the usefulness of hormonal therapy.

TABLE 10.—*Averages of Free Interval for Three Groups*

Patients, No.	Group	Mean, Mo.	Standard Deviation, Mo
124	B1	31.36	33.77
48	B2	87.10	57.25
377	B3	39.19	36.60

Evidence of progressive disease before starting treatment was not required. This was compensated for by designating as nonresponders those 29 patients whose disease remained static during treatment and follow-up, thus lumping them with the failures in this evaluation of the effectiveness of hormonal therapy. To do otherwise would require a largely artificial grouping of patients with static or "arrested" disease, contributed to in some part by the phenomenon of spontaneous arrest. The experience of the subcommittee, which led to the most elementary classification of "responders" and "nonresponders" as employed here, by rigid criteria of objective improvement, also suggests that more divisive groupings with such terms as "arrested," "remission," and "equivocal" are of dubious value.

In the analysis of responsiveness of postmenopausal patients to treatment, the samples were limited, in most instances, to those women who had experienced a natural climacteric. The intent was to obtain groups as homogeneous as possible for such comparisons, and, in a significant number of those whose "menopause" had been induced, the cessation of the menses was attended by uncertainty of the artifactive process used. Most frequently a pelvic operative procedure followed by amenorrhea was not accurately recorded as including ovarian ablation. In other instances, pelvic irradiation apparently had resulted in amenorrhea, but, without details of tissue (midpelvic) dose, no impression of the physiological effectiveness of this measure was possible. Actually, when the induced-menopause group was combined with the natural postmenopausal patients, and the aforementioned calculations repeated, there was no significant variation between the total postmenopausal "population" and the more physiologically homogeneous fraction.

Indications of Variations in Natural History of Mammary Carcinoma

Several trends which emerged during this review are reflections of the variable natural history of mammary carcinoma, apart from their correlation with the results of hormonal treatment.

Free Interval.—A phenomenon of intriguing interest to any observer of the clinical course of cancer of the breast is the activation of metastatic disease after many years of good health following eradication of the primary growth in the breast. Late manifestations of metastasis are so common that the traditional yardstick of survival for five years is of little value; it is not uncommon for the initial evidence of distant spread to appear 15 to 20 years after definitive, primary treatment, and in one carefully studied and verified instance the first local (axillary) recurrence was noted after 37 postoperative years. The lapse of time between primary, definitive treatment (usually mastectomy) and, in this view, the initial use of hormonal therapy is an approximate index of the latent period of foci of metastasis and necessarily must be an expression of the biological balance between host and neoplasm. The time during which metastasis remains occult, or subclinical, is referred to hereafter as the free interval.

A number of analytical procedures have been applied to available free-interval data, one of which indicated a natural division of the sample at hand into three groups. In the first group, both primary treatment and metastatic growth occurred prior to the menopause (designated B1); the second group had mastectomy prior to the menopause and recurrence after a natural climacteric (B2); the third group was comprised of those in whom a natural menopause preceded both primary disease and appearance of metastasis (B3). The free-interval averages for these three groups are shown in table 10. Each of these average values is statistically different from each of the other two: $p<0.05$, comparing group B1 with group B3, and $p<0.001$ for the other two comparisons. (These statistical statements are made on data from which "untreated primaries" and "induced-menopause" groups were excluded. Cases treated with androgen or estrogen, responders or nonresponders were pooled.)

The identification of the B2 group, characterized by an inordinately long free interval averaging 87 months (7¼ years) and by the interposition of the menopause between primary treatment and metastatic activity, represents a unique and hitherto unrecognized, though minor, fraction of patients in whom the natural history is so disparate as to require its separation from the major groups of cases.

Table 11.—*Comparison of Relative Frequency of Regression by Free Intervals and Hormone Treatments*

		Free Interval, 0-36 Mo.			Free Interval, 37+ Mo.				
		Patients,	Regressions		Patients,	Regressions			
Group*	Treatment	No.	No.	%	No.	No.	%	χ^2	p
A. All cases	Androgen	132	24	18.2	98	35	35.7	8.168	<0.005
	Estrogen	106	31	29.2	90	33	36.7	0.901	...
B. Only B2	Androgen	43	10	23.2	28	15	53.6	5.584	<0.025
	Estrogen	31	7	22.6	29	9	31.0	0.201	...
C. Without B2	Androgen	89	14	15.7	70	20	28.5	3.121	<0.075
	Estrogen	75	24	32.0	61	24	39.3	0.505	...

* Natural menopause cases only.

All prior studies with which the subcommittee is familiar have indicated comparably longer free intervals in patients who were older by either chronological or endocrinologic landmarks. This concept may be derived also from the study at hand, in which the average free interval of 124 premenopausal women was 31.4 months, whereas it was 44.6 months for 425 patients whose menopause had occurred spontaneously. Recalculation of free interval for the postmenopausal group after removing the influence of the B2 patients (i. e., all postmenopausal patients minus the B2 group, leaving residual B3 group), demonstrates a diminished free interval for these 377 women of 39.2 months, which is more comparable to the figure for premenopausal patients.

To explore the possibility that the effectiveness of hormone therapy might be related to duration of the free interval, it was tested for correlation, with two indexes of response. The correlation of the incidence of regression with increasing length of free interval was found to be significant ($r_{pb}=0.081$, $p<0.05$). Correlation of the length of free interval with duration of survival after beginning hormone therapy was also very significant ($r=0.138$, $p<0.01$) for the 518 cases with the necessary information. This correlation was significant, even when the test was applied separately to responders and nonresponders.

Because the free interval appeared to have some prognostic value, its association with the age of the patient at definitive treatment of the primary lesion was tested. Significant inverse correlations were found between these two values for 123 patients in whom primary treatment and metastasis preceded the menopause ($r=-0.248$, $p<0.01$), and for 375 patients whose primary and palliative therapy both followed a natural menopause ($r=-0.142$, $p<0.01$). This is to say that the younger the patient is at the time of recognition and treatment of her primary disease the longer the evidence of metastasis is likely to be postponed.

That the average free interval for the B1 group was 31.4 months and for the B3 group was 39.2 months does not contradict the surprising inverse relationship described. Although the average age and average free interval were both smaller in the B1 group, the statistical examinations produced significant inverse correlations, whether performed on data within each of the two groups or on the two groups pooled.

The unusually long free interval seen in the small B2 group suggests that in these patients there was some unusual biological or metabolic feature which favored a very long occult phase of metastatic disease. Nonetheless, the inverse correlation between primary age and free interval in this group was also significant ($r=-0.439$, $p<0.01$).

In analyzing the inverse relationship between the free interval and age, it became desirable to determine the influence of this interval on rates of regression in the B2 group, in view of postprimary free periods of such remarkable length, and to discover what differences might exist between the B2 cases and all other naturally postmenopausal women. Analyses of the entire series of naturally postmenopausal patients (at the time of beginning hormonal therapy), by division of androgen-treated and estrogen-treated groups into subgroups of free intervals through 36 months in duration and 37 or more months, appear in table 11. By this arbitrary subgrouping, the association of the longer free interval with a greater percentage of regressions was highly significant for those treated by androgens but was not statistically significant in those given estrogens.

The same analyses for the B2 group and for the remaining patients (131 and 295 cases respectively) of the naturally menopausal series are presented separately in B and C of table 11. Again, the longer free interval was unassociated with any significant increase in the occurrence of regression with treatment by estrogens. In both larger and smaller groups, the influence of the longer postprimary free interval was significant with androgenic therapy, although not as striking by statistical standards.

Table 12.—*Vertical Comparisons of Table 11*

	Free Interval,	Regressions			
Group	Mo.	Androgen, %	Estrogen, %	χ^2	p
A. All cases	0-36	18.2	29.2	3.451	<0.06
	37+	35.7	36.7	...	...
B. Only B2	0-36	23.2	22.6	...	...
	37+	53.6	31.0	2.129	<0.250
C. Without B2 ..	0-36	15.7	32.0	5.172	<0.025
	37+	28.5	39.3	1.250	...

It is revealing to examine the same data from another perspective, as shown in table 12. In the group from which the B2 cases were excluded, t frequency of regressions was significantly greater ($\chi^2=5.172$, $p<0.025$) among the estrogen-treated women than among the androgen-treated women whose free intervals were less than 37 months. If the values comparing androgen and estrogen effect are compared when the free interval exceeds 37 months, statistics indicate they are not different.

Within the B 2 group, androgen and estrogen were found to elicit equal frequencies of regression when the free interval was less than 37 months. After 37 months, a greater frequency of regression occurred after androgen treatment than after estrogen therapy (though it is statistically insignificant).

Comparing the frequency of regression under different treatments and by the arbitrary free-interval separation at 36 months, androgen was superior, though not statistically, to estrogen only when 53.6% is compared to 31.0%. Within the androgen-treated group the regression group is greater among the B2 group (53.6%) than in the B3 group (28.5%) when the free interval is more than 37 months ($\chi^2=4.41$, $p<0.05$). Thus, it is possible to suggest that, in a B2 patient who had a free interval longer than 3 years, androgen is more likely to be of benefit than if she were not in the B2 group. These data do not show that androgen will be any more favorable to this B2 patient than will estrogen.

An even more valid endorsement of the prognostic value of the free interval was its significant correlation ($r_pb=2.25$, $p<0.025$) with the incidence of regression.

Survival.—The most significant and most consistent phenomenon in the behavior of the disease under hormonal treatment, both by androgen and estrogens, was the increased survival time of patients in whom objective regression of disease occurred (tables 6 and 8, fig. 3). It should be noted that the nonresponsive groups, whether premenopausal or postmenopausal, whether treated by androgens or estrogens, and whether postoperative or with primary neoplasm *in situ*, had average survival periods in a narrow range of 8 to 11 months after starting treatment. When the status of the primary site was disregarded, the over-all mean survival time for the premenopausal and androgen-treated or estrogen-treated postmenopausal groups was 11 months, 10 months, and 11 months respectively. These short, statistically equivalent periods of survival in nonresponders provided highly dependable base lines, consistent with the natural history of untreated disease in these groups (see below), against which the responders survived for average intervals of 18, 20, and 27 months respectively. Statistical significance of the disparity in survival of responders and nonresponders was at the critical level of $p<0.001$ in comparing four of the six subgroup pairs shown in table 6 and was within the area of confidence for data of this type in the other comparisons, considering the over-all trend.

The capacity for objective regression of neoplasm and the associated increase in survival which differentiated responders from nonresponders were important indications of fundamental biological differences between the two groups. The evidence of basic disparity was not so much in the presence or absence of tumor-suppressive effect as in the fact that regression was followed by a significant alteration in the course of the disease and in survival, whereas, without regression, the pattern of disease and survival remained unaltered. The significance of the data supporting this basic separation of patients provides both incentive and promise to efforts in research aimed at the elucidation of hostal or tumoral factors responsible for these reactions.

Results of Treatment

Distribution of Patients.—There were only 167 premenopausal women, compared to 777 postmenopausal patients, making up the total of 944 available for analysis. Of these, 580 were treated by androgens and 364 by estrogens, a resounding vote for androgenic substances, justification for which is lacking in the data presented herein. If a conclusion stated earlier had been followed in this series, namely, that estrogens are more effective than androgens after the fourth postmenopausal year, the ratio of their use would have been reversed, and 588 would have been treated with estrogens (table 4).

Although those treated by androgen were of an average age (51 years), 12 years less than the estrogen series (63 years), the difference was more chronologic than endocrinologic, and there was obviously a lesser disparity (6 years) in age by years in the only patients for whom such comparison was proper—those who were postmenopausal.

Of the 716 postmenopausal women for whom the elapsed years of diminished ovarian activity were recorded, there were 167 in whom the menopause had been induced prior to the activation of metastasis. Of these, 115 were treated by androgens and accounted for 21.3% of all patients so treated; 52 of the estrogen series, or 15.9%, were treated after an induced menopause. This distribution is reasonably analogous to the over-all androgen-estrogen ratio; e. g., 38.5% (364) of the total of 944 patients and 31.1% (52/167) of the induced menopausal group were treated by estrogens.

Chronological Age: As seen in figure 4, too few patients were treated with estrogens before age 40 to allow any comparison. It is no surprise that in women past 70 years of age estrogens were of significant superiority ($p<0.02$). In the decades from 40 to 50, 50 to 60, and 60 to 70, estrogenic therapy produced greater percentage rates of regression; although these were not statistically valid, the approximate number of regressions per 100 patients, estrogens over androgens, was 29 and 16, 30 and 24, and 37 and 31 respectively. This consistent superiority of estrogen through all ages past 40 gives no indication that the performance of androgenic therapy was at a disadvantage due to factor of age.

Endocrinologic Age: In table 4 a review of percentage rates of regression, noted in successive periods beyond the menopause, shows that the estrogens reach a plateau of performance after the fourth postmenopausal year, with about 38 of every 100 patients obtaining regression. The androgen series records a similar plateau, but at a later phase, or after the eighth postclimacteric year, and at a less effective level than with estrogens, with regression occurring at a rate of nearly 27 of each 100 patients. On cross comparisons of differences within each of the two treatment series, significant values were found only between the intervals zero through four years and five through eight years among the estrogens ($\chi^2=4.804$). The possibility that the androgens are at a disadvantage due to their use in women who are younger than those in the estrogen series becomes less credible when the effectiveness of androgens at the two extremes of age is examined. In premenopausal patients in the decade from 31 to 40 years, androgens induced regression in 21.4% of 84 patients. In a group of patients aged 71 to 95 years, 21 were subjected to androgenic therapy and only 4, or 19.0%, experienced any regression. The corresponding regression rates for estrogens were 28.6% for those aged 31 to 40 years (postmenopausal women) and 51.5% for the oldest grouping.

Although the differences in these rates of regression are of statistical significance only in the postmenopausal interval of five through eight years (table 4), the consistent disparity is not without practical clinical overtones, which are amplified to a degree of real significance by considering larger samples, as in table 7. Here it is shown that, in the period ending with the eighth postmenopausal year, estrogens produced a 27.0% regression rate to 16.3% for androgens ($p<0.06$); during the years thereafter, the comparative rates were 37.7% and 27.7%, a significant difference of $p<0.05$. Inasmuch as an equally significant difference was demonstrated in the smaller samples (table 4) for the fifth through the eighth year after the menopause, it is reasonable to conclude that, in all women more than four years postmenopausal, the performance of estrogens is distinctly superior.

A recommendation that estrogens be used prior to five or more years after the menopause will seem hazardous to many clinicians, for some authors continue to sound warnings against their use for a full decade beyond the climacteric. The persistent apprehension which attends the therapeutic use of estrogens is accounted for by a number of factors: the emphasis on androgens only in the early years of treatment by hormones (1940-1945), uncertain knowledge of the role of endogenous estrogens in the genesis of breast carcinoma in human and animal varieties, and the popularization of the concept of "estrogen-dependency" in recent years. This is, however, an appropriate reminder of an obligation to emphasize again that "therapeutic" amounts of any estrogenic substance in the menstruating woman may be followed by augmentation of breast carcinoma. Several of the investigators associated with this study in its early years had the misfortune of observing acceleration of the growth and spread of the neoplasm concurrently with estrogenic therapy. Of the seven premenopausal patients of this series given estrogen, all exhibited progression, but this is not to say that all, or even any of them, were in a true phase of augmentation as distinct from the behavior of the disease in an unfavorable, rapid pattern of growth of natural origin.

Sites.—In the consideration of effectiveness by location of metastasis in patients with dominant involvement in single systems, there were no statistical differences of really critical degree in either the androgen or the estrogen series (table 5). In terms of practical probability, androgens were of lesser efficacy before a natural menopause than afterwards in metastasis to bone. For all cases, there was a striking similarity in the androgen-associated regressions in the three systems.

For estrogens, the greatest percentage of regression for the natural postmenopausal women occurred in soft tissue deposits. Regression of 40.7% of soft tissue lesions in elderly women seems more notable than the 31% control of visceral and osseous spread.

When a comparison of androgens and estrogens was limited to their effectiveness in the homogeneous group of natural postmenopausal women, regression in practically identical proportions was noted for both visceral and skeletal locations with the use of each type of hormone, or in 31 of each 100 patients. The greater control of metastasis in soft tissue by estrogens is again apparent, or in 41 of each 100 patients, compared to 18 of each 100 with use of androgens ($\chi^2=4.347$, $p<0.05$). The observation of greatest practical importance is an equally effective control of skeletal metastasis by androgens and estrogens. The notion that the andogens are of greater value at all ages for bony involvement is still widely entertained. For postmenopausal patients, many clinicians cling to a routine of using estrogens for soft tissue and visceral spread and androgens when skeletal involvement is demonstrable; the fallacy of this approach is indicated in the inconsequential difference of 0.9%.

Survival.—In responsive patients, average survival time of the estrogen-treated (table 8) is significantly longer than that of the androgen-treated. This demonstrates a more effective antitumoral function for estrogens in their contribution to greater longevity, of very significant degree in estrogen responders ($p<0.005$). Although the disease becomes less lethal with increasing time beyond the menopause, the criterion of the free interval is less favorable than in premenopausal women, as outlined earlier. The older woman therefore realizes longer survival than the younger, on the average, but she also tolerates the presence of clinically detectable cancer for a greater fraction of that increased life span. This is a denial of the usual concept that both types of hormones became more effective by reason of a predominant trend of aging women to develop neoplasms of a less aggressive pattern generally. Such a concept is now inadequate, to the extent of our recognition of earlier metastatic activity and a longer time of active growth (shorter free interval) than in the younger woman, and to a similar extent that estrogens and androgens must both be credited with a greater degree of carcinostatic potency. Further, the estrogens now must be recognized as inherently superior to androgens in a qualitative fashion and by a significant degree.

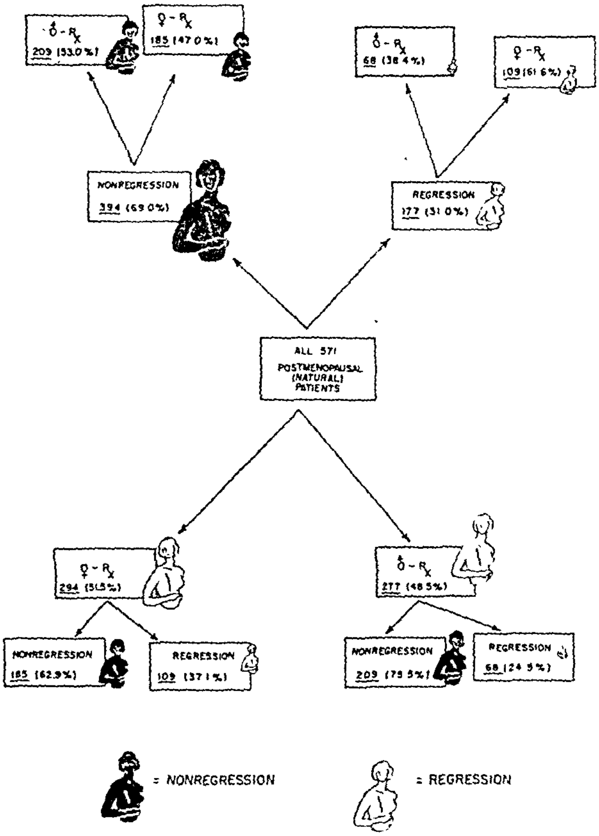

Fig. 5.—Incidence of response to treatment of natural postmenopausal patients.

Summary of Comparative Effect—Androgens and Estrogens.—There can be no reasonable doubt concerning the advantage of estrogens in the initiation of regression in postmenopausal women. For a final look at comparative performance, there are striking features in the data in table 6 and figure 5. Of the 571 natural postmenopausal women there are less than 5 chances in 1,000 that estrogen superiority in either grouping is coincidental.

In brief, at all ages past 30 (if the patients were postmenopausal, either induced or natural), at all phases of postmenopausal life, in each anatomic spread to single systems, and by average duration of life in responsive women, estrogens were equal to androgens, and more often of some advantage, in the frequency with which their use was associated with objective regression. The instances in which calculations indicated roughly equal rates of regression for both groups of hormone-treated patients were as follows: during the period of zero through four years after the menopause, in most of skeletal spread, and in visceral foci in (natural) postmenopausal women. At all other chronological and endocrinologic intervals (except, of course, the premenopausal) and in other situations of unisystemic metastases, the results were at least presumptive of a greater effectiveness for estrogens. Although the differences were of statistical significance less often than of an apparent, percentile order, there were instances in which consolidation to produce a larger sample or a more homogeneous group provided statistical validation at critical levels.

Side-effects.—A final consideration of considerable importance to the physician in his selection of hormonal agents, and of still greater moment to the woman with disseminated carcinoma of the breast, is a comparison of the extreme physiological effects on various target tissues, or side-effects, of the two groups of substances. In the physiologist's orientation, the tumor-suppressive action is the "side-effect," but the most favorable endocrinologic milieu for maximum rates of regression requires doses of a magnitude commonly producing the clinician's "side-effects." In clinical thinking this term does not include such favorable phenomena as the anabolic or hematopoietic effects but indicates rather the distressing manifestations, which, in general, are due to either virilization or feminization, the anorexia, nausea, and vomiting much more common with estrogens, the hazard of hypercalcemia, which is likely to be more frequent with androgens, and many others.

Although a review of side-effects has not been a part of the current study, progress reports of the subcommittee, based largely on the same series of patients reported here, have detailed their incidence and significance.[2] A comprehensive review of the subject was published in 1953 by Kennedy and Nathanson,[3] as an informative document ancillary to the published data from this subcommittee.

With this evidence of prior interest in the problems of side-effects and the study and publication of data pertaining to the series reported here, it is the consensus of the subcommittee that the distressing physical, psychic, and emotional side-effects of the androgens were of greater magnitude than were those of the estrogenic substances, in the doses required for the therapy of cancer. The dilemma may be epitomized by stating that a biological system conditioned for a dominant response to feminization will tolerate more kindly the insults of its untimely resurgence than it will the physiological travesty of a reversal in sexual polarity.

If this philosophy born of clinical experience is valid, a preference for estrogenic therapy is obvious whenever the probability of regression is equal, or superior, to that which may be secured by the use of androgens. Specifically, the results of this study indicate that all patients beyond the fourth postmenopausal year (or, perhaps, even earlier after the climacteric) should have initial hormone treatment by estrogens.

Summary

Reports on a series of 944 women with disseminated mammary carcinoma treated by androgenic hormones (580 women) and estrogenic hormones (364 women), from 1947 through 1956, by 60 participating investigators, have been subjected to reanalysis and an evaluation of the results. The follow-up, until time of death or the date of the analysis, was successful in 89.4% (844 women). Androgens produced objective regression in 20% of premenopausal patients and in 21% of postmenopausal women. Estrogens, limited properly to postmenopausal patients, induced regression in 36% of patients. Both types of hormones were more effective after the eighth postmenopausal year, at which time both reached a plateau of performance, but with the estrogens inducing a higher relative frequency of regressions (38%) than did the androgens (27%).

In cases with unisystemic dissemination, estrogens produced a greater degree of control in soft tissues at all post*menopausal* ages and were equal, or superior, to androgens for skeletal and visceral metastasis.

Responsive patients had significantly longer survival rates with androgenic or estrogenic therapy, whereas the unresponsive women with either mode of therapy had almost identical average periods of survival comparable to untreated patients. Steroid sex hormones are sufficiently effective in naturally postmenopausal women to deserve a primary trial in the treatment of disseminated *mammary carcinoma*. After the fourth postmenopausal year, estrogenic substances are the agents of choice.

The hormonal substances used in this study were supplied by Abbott Laboratories, North Chicago, Ill.; Ayerst Laboratories, Inc., Division of American Home Products Corporation, New York; Ciba Pharmaceutical Products Inc., Summit, N. J.; Charles E. Frosst & Co., Montreal; Lakeside Laboratories, Inc., Milwaukee; The Wm. S. Merrell Company, Cincinnati; Organon, Inc., Orange, N. J.; Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.; Rare Chemicals, Inc., Harrison, N. J.; Schering Corporation, Bloomfield, N. J.; E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, New York; The Upjohn Company, Kalamazoo, Mich.; Maltbie Laboratories Division, Wallace & Tiernan Inc., Belleville, N. J.; White Laboratories, Inc., Kenilworth, N. J.; Winthrop Laboratories, New York.

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HOW THE KIDNEYS GOVERN THE DISTRIBUTION OF WATER.—In the intact animal with metabolism proceeding steadily, extracellular osmolarity controls the water balance of the cells. Hence thirst and water diuresis, which rather precisely guard against excessive or deficient levels of extracellular osmolarity, may be regarded as mechanisms controlling the volume of intracellular fluid. Since they do this by stabilizing an extracellular osmolarity which is mostly due to sodium salts, they also set the stage for the regulation of extracellular fluid volume by adjustments of the renal excretion of sodium. For so long as its osmolarity is held constant, the volume of extracellular fluid must be proportional to the amount of sodium which it contains, and this depends upon how much of the daily intake the kidneys retain. Hence the kidneys, directed in ways which largely remain to be elucidated . . . are able to regulate the volume of water inside the cells by controlling the excretion of water, and the volume outside the cells by controlling the excretion of sodium. . . . Thus the organization of intracellular as well as of extracellular fluids, together with the exchanges both between compartments within the body and between the body and the external environment, may be described to a remarkable extent, in Gamble's . . . happy phrase, as a "Companionship of water and electrolytes."—J. R. Robinson, Metabolism of Intracellular Water, *Physiological Reviews*, January, 1960.

PRELIMINARY COMMUNICATIONS

MANAGEMENT OF DELIRIUM TREMENS

PRELIMINARY OBSERVATIONS WITH TRIFLUOPERAZINE

Naseeb B. Baroody Jr., M.D., Waddy G. Baroody Jr., M.D., Adrian Reed, M.D.
and
Walter R. Mead, M.D., Florence, S. C.

One of the commonest problems confronting the practicing physician today is alcoholism. Treatment of the patient with alcoholism encompasses not only the acute phase but also the chronic cases, which may include patients with the difficult problems of hallucinosis and delirium tremens. Alcoholic withdrawal, when complicated by acute hallucinations, disorientation, excitement, and hyperkinesia, is a difficult condition to manage in the average general hospital, unless the hospital is equipped with specific facilities for handling confused, disoriented, and perhaps belligerent patients. For this reason, or excuse, many general hospitals refuse admission to alcoholic patients; often physicians too may be guilty of shunning the alcoholic patient and refusing to accept him psychologically or realistically as a sick person in need of hospital care. For the alcoholic, withdrawal is a serious metabolic disorder involving basic abnormalities in glucose and vitamin metabolism, nutritional disturbances, and less understood enzymatic and biochemical alterations.

Perhaps if we were better equipped therapeutically to detoxify alcohol rapidly, prevention or control of the withdrawal syndrome (hallucinations and delirium tremens) might be possible, and we might be less reluctant to accept and to treat this disease. It is toward this end, therefore, that we have directed our efforts in this study.

The "habit patterns" of alcoholics are important in withdrawal. Alcoholics who hallucinate or develop delirium tremens are usually chronic or recurrent drinkers of at least five years' duration. After years of nonhallucinatory withdrawals they suddenly develop a new postalcoholic or withdrawal pattern. Hallucinations or delirium tremens dominate and complicate this postalcoholic period, and, once manifest, their recurrence can be accurately predicted and anticipated after future alcoholic debaucheries. Unfortunately, the habit pattern will usually persist regardless of the duration of intervening sobriety. Awareness of this pattern is of great value in knowing what to expect during the withdrawal period, and, when armed with this information, one is equipped to direct the therapeutic regimen more effectively.

Syndrome of Delirium Tremens

Delirium tremens is a fairly common syndrome, a result of prolonged drinking and of alcoholic withdrawal which usually comes on after the patient is detoxified. It may be preceded by a period of lucidity and apparent although agitated normalcy lasting from 48 to 72 hours. It may be precipitated by a variety of factors which include high fever, infections, injuries, exposure, anesthesia, and vigorous exercise. Delirium tremens is characterized by disorientation, confusion, hallucination, coarse tremor, hyperkinesia, and intense excitement. Actually, it is a hallucinatory delirium with marked general tremor and toxic symptoms. The hallucinations are vivid and frequently predominate at night or when the eyes are closed. They often assume the form of bizarre, usually large and fast-moving, animals, or animal-human combinations, similar to those seen in today's currently popular horror movies. Auditory delusions or hallucinations are less common and are usually in the form of human voices, with threatening conversations. In addition to these symptoms patients exhibit a coarse, arrhythmic tremor of the tongue, face, fingers, legs, and occasionally trunk, and generalized epileptiform seizures may occur. These patients occasionally exhibit marked disturbances of equilibrium and bodily orientation. Disturbances of the autonomic nervous system are common.

The differentiation of delirium tremens from alcoholic hallucinosis is frequently difficult (fig. 1). Block [1] defined alcoholic hallucinosis as a syndrome of alcoholic withdrawal characterized by visual or auditory, or both, hallucinations. With the addition of mental confusion and disorientation, according to Block, the diagnosis becomes delirium tremens. In our experience, there is considerable overlapping of symptoms, many of which are fleeting and transitory. For example, confusion and disorientation in hallucinosis may become most prominent at night,

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From the Department of Medicine, the McLeod Infirmary.

with considerable clearing and reorientation during the day. We have found the most reliable differentiation between hallucinosis and delirium tremens to be the presence or absence of hyperkinesia and excitability. With delirium tremens, patients are not only confused and hallucinating but they also exhibit extreme motor irritability, agitation, and excitement. They are frequently frightened, may become belligerent and difficult to manage, and may require restraints and constant nursing care. Convulsions are not uncommon and may result in tongue chewing or other bodily injury due to falls.

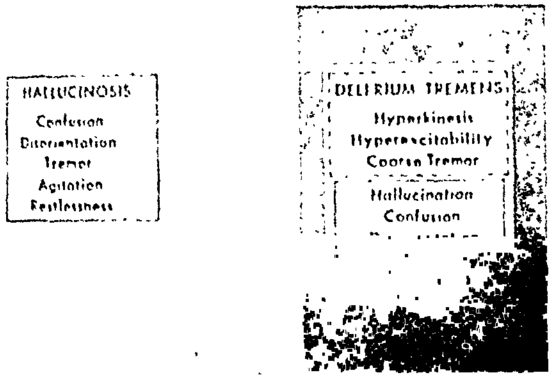

Fig. 1.—Symptoms of alcoholic hallucinosis and of delirium tremens, showing overlapping of symptoms.

The frequency with which delirium tremens occurs is extremely difficult to determine; however, the magnitude of the alcoholic problem leads to the inevitable conclusion that it represents a serious challenge to all who recognize and treat alcoholics. Further evidence of the seriousness of delirium tremens is supported by reported mortality statistics of from 5 to 15%.[2] Only subsequent to the availability of newer therapeutic agents and a better understanding of the altered pharmacodynamics of the disease has the mortality been reduced.

Until recently, the morbidity varied from one week to three weeks, with the acute brain syndrome lasting, on the average, for five to seven days. Newer therapeutic agents have reduced the period of active delirium tremens to an average of three to five days, with total period of hospitalization lasting proportionately less.

Present Study

Material and Method.—Trifluoperazine (Stelazine) is a phenothiazine derivative. Because it has been reported to have antihallucinatory effects in psychotic patients,[3] we conducted a preliminary trial with the drug in 23 alcoholics. In all of these 23 patients the problem of hallucinosis or delirium tremens was either present during hospitalization or indicated by their history. Immediately after their admission to the hospital all patients routinely received parenterally administered chlorpromazine or promazine along with intravenously given fluids, electrolytes (including magnesium), glucose, and vitamins. If there was a history of delirium tremens, trifluoperazine administration was begun on admission. If not, it was withheld until the first sign of actual or impending mental aberration was observed, at which time these patients were given trifluoperazine intramuscularly in doses of 2 mg. every six hours. This dose was reduced to 2 mg. every eight hours when symptoms were better controlled. Later, on cessation of delirium tremens, the dosage of trifluoperazine was changed to 10 mg. given orally three to four times a day. Orally given medicaments were of no value in the acute hallucinatory stage.

Results.—Our past experience indicated that in patients receiving routine therapy with fluids, electrolytes, promazine or chlorpromazine, and vitamins, delirium tremens usually lasted from three to five days. Although symptoms were markedly decreased, the natural course of this illness seemed altered little by these medications. In contrast to this, however, this study (fig. 2) revealed that of the 10 patients who hallucinated, none was disturbed for more than three days and 7 were reoriented in less than three days. In this group the average duration of delirium tremens was only one and four-fifths days. Thirteen had no hallucinations at all, although they gave a history of them with previous alcoholic bouts.

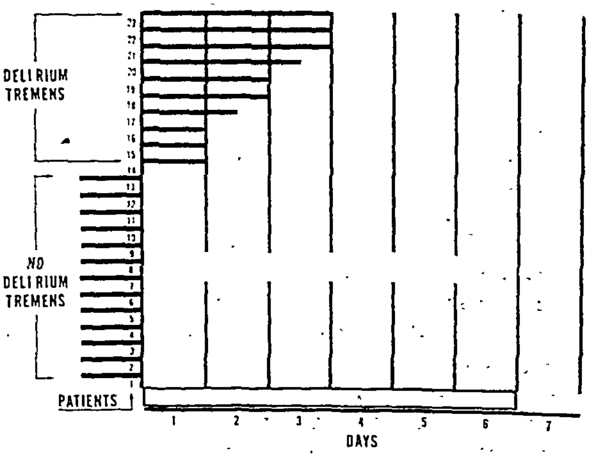

Fig. 2.—Duration of delirium tremens: summary of results obtained in 23 alcoholic patients receiving trifluoperazine. All patients had either history of delirium tremens or symptoms on admission. Axis of abscissas represents average duration of delirium tremens as reported in literature.

Report of a Case.—A dramatic instance of the effects of trifluoperazine is presented by the case report (fig. 3) of a 63-year-old man, an alcoholic of many years' standing. Previous admissions had been characterized by marked disorientation, confusion, hallucinosis, and hyperkinesia. On the first admission of this study the patient had been drinking heavily for about one week and was extremely restless and agitated. He was treated on admission with glucose, vitamins, fluids, electrolytes, promazine, and chlorpromazine. Hallucinations began 48 hours after admission and were quickly followed by marked disorientation, hyperkinesia, excitability, and tremor. Restraints were required. Once he began to hallucinate, azacyclonol hydrochloride (Frenquel) was given intravenously. Delirium tremens continued, however, and restraints were necessary for about six days before spontaneous improvement occurred.

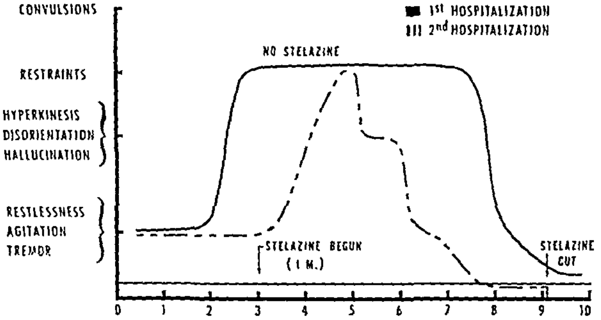

Fig. 3.—Case summary of 63-year-old alcoholic man with recurrent history of delirium tremens after each withdrawal. Axis of abscissas represents days of hospitalization.

On the patient's second admission a similar history of prolonged alcoholism was obtained. He was admitted in a state of restlessness, agitation, and tremor. He remained oriented until the third hospital day when be began to hallucinate and became disoriented and markedly hyperkinetic. At this point, trifluoperazine was given, 2 mg. intramuscularly every four hours. He became difficult to manage and restraints were required, for one night only. Despite continued hallucinations, he was much more manageable and would sit quietly in bed or in his room. Hyperkinesia was minimal. Within 72 hours he was once again oriented and exhibited only some restlessness and slight tremor.

Comment

The basic cause of delirium tremens is not known. Many factors (fig. 4) related to alcoholic intake and metabolism have been identified and investigated. Perhaps the most popular and best studied aspect is vitamin deficiency combined with altered carbohydrate metabolism.

In patients with alcoholism there is impairment of intake and absorption of carbohydrates and vitamins. Thus, the carbohydrate respiration of brain tissue, in which vitamins are essential, is put under stress. The oxidation of alcohol requires thiamine. This vitamin is in priority demand and may result in quick depletion of the body's available thiamine chloride so necessary for glucose metabolism by the Krebs cycle.[4]

Mineral deficiencies, particularly of magnesium, occur in patients with chronic alcoholism. Recent studies[4,5] have shown that magnesium deficiency may cause gross muscle tremor, choreiform movements, and occasionally delirium and convulsion. Magnesium is necessary for the action of a number of enzymes, particularly adenosine triphosphate (ATP).

"Hyper-hydremia," with resultant cerebral edema, is a recognized pathological finding in patients in an acute alcoholic state. This results in a high concentration of alcohol in the cerebral cortex, with subsequent interference of enzyme systems, particularly hydrogenase, similar to the action of narcotics and anesthetics.[6] All of these pathogenic factors become greatly exaggerated and magnified in the presence of altered liver function, whether it is due to simple fatty infiltration or to the more serious advanced alcoholic cirrhosis.

Current experimentation indicates that the basic defect in patients with delirium tremens occurs at a cellular level. Grenell has shown that in the alcoholic brain there is alteration in the structure, biosynthetic mechanism, and membranes of brain cells. This results in changes in cell membranes followed by cellular volume changes, inhibition of electron transfer, alterations of structure, greatly decreased esterification of inorganic phosphates, and inadequate synthesis and utilization of the external adenylic system to maintain normal structure.[6]

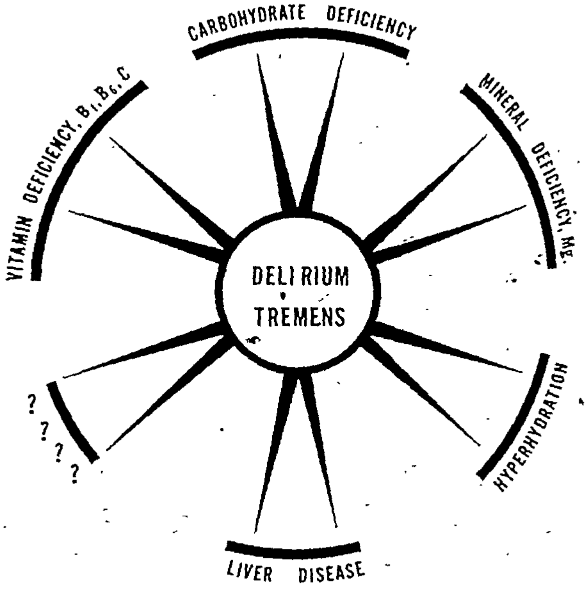

Fig. 4.—Factors related to pathogenesis of delirium tremens.

Treatment.—The essential management of patients with delirium tremens is directed toward correction of the above described pathophysiological factors (fig. 5). The administration of an electrolyte solution containing glucose maintains nourishment and proper fluid balance. Flink [5] has reported magnesium therapy to be of significant value in the treatment of delirium tremens. An electrolyte solution containing magnesium may be used. Vitamins are administered in large doses, with particular emphasis on replacement of the B complex group, especially thiamine. Insulin, once given as a part of accepted therapy, for the quicker detoxification of alcohol, is now considered of little physiological use. Insulin is not required by brain cells and, indeed, the beneficial hyperglycemia may be annulled by it.[4] Steroids have been reported of benefit in the management of acute delirium tremens.[7] Their use is directed at supporting the extreme physiological stress encountered. Diuretics have been administered, in an effort to diminish the hyper-hydremic state and, particularly, cerebral edema.

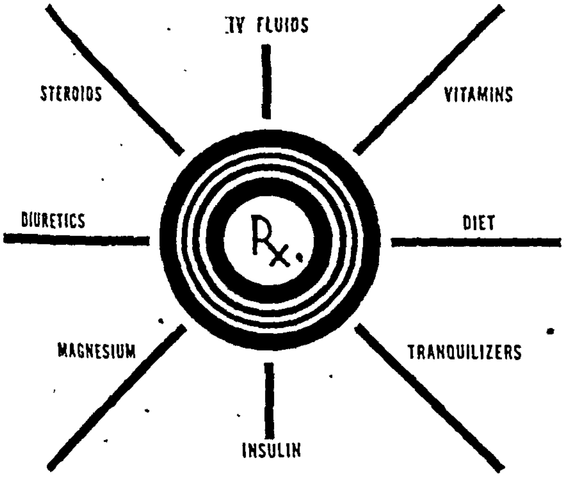

Fig. 5.—Basic principles in therapeutic management of patients with delirium tremens.

Tranquilizers have revolutionized the treatment of alcoholism.[8] Most benefits have been derived from the use of phenothiazine derivatives. Although these are useless in the initial phase of alcoholic depression, they are extremely valuable assets in the management of the agitation and restlessness of withdrawal. They produce relaxation and reduce tension, allowing the patient to resume a state of normalcy more quickly. Despite their beneficial effects, however, we have not found the incidence of hallucinosis to be significantly diminished by their use. In large and frequent doses, phenothiazine derivatives may be valuable in controlling the extreme hyperactivity of delirium tremens; however, in our experience they do not shorten the duration of this serious complication.

Summary

Delirium tremens is a serious complication of withdrawal of alcohol, in alcoholic patients, which carries a reported mortality of from 5 to 15%. The differentiation of hallucinosis from delirium tremens is not always clear-cut. Although all of the causative factors are not known, they include vitamin deficiency (especially of thiamine), carbohydrate deficiency, magnesium deficiency, liver disease, "hyper-hydration," and alterations in the cell membranes of the brain. Therapeutic principles include the administration of glucose, vitamins, magnesium, diuretics, tranquilizers, and steroids.

We have found trifluoperazine, administered intramuscularly in doses of 2 mg. four times a day, to be an effective therapeutic measure when added to the accepted treatment for delirium tremens. Orally given trifluoperazine was found to be of no value in the acute hallucinatory stage. No toxic reactions or side-effects due to trifluoperazine were observed in the patients studied. Further investigation is required to better establish the optimal dosage of trifluoperazine in patients with delirium tremens.

376 W. Palmetto (Dr. N. B. Baroody).

The trifluoperazine used in this study was supplied as Stelazine by Smith Kline & French Laboratories, Philadelphia.

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THE JOURNAL
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SEX STEROIDS FOR PALLIATION OF DISSEMINATED MAMMARY CARCINOMA

GUEST EDITORIAL

Ian Macdonald, M.D.

ELSEWHERE in these pages is the final report of a pioneer effort in the pooling of clinical data from a cross-section of investigators in the United States and Canada, the intent of which was to replace confusion with some degree of clarity in a "new" area of cancer therapeusis. Although the use of estrogenic and androgenic hormones for palliation of mammary carcinoma is no longer new, as it was when the Committee on Research initiated this study in 1946, some of the prejudices and mistaken practices current then seem to be almost as prevalent now. The primary benefit of a cooperative study should be an accumulation of comparable data, on samples of significant size, long before the individual investigator or institution can acquire the experience necessary for valid reporting. The Subcommittee on Breast and Genital Cancer, which is responsible for this study, has published various reports; however, the final evaluation has been long delayed because of early failures in planning common to initial ventures of this sort.

More than two years ago it was finally realized that a reanalysis and recoding of reports on over 1,900 patients was required, that the interpretation of the reports required the contribution of a clinician conversant with the natural history of carcinoma of the breast, that additional follow-up of many patients was essential for maximum salvage, and, finally, that a sophisticated treatment of the data demanded discriminating biostatistical consultation rather than an undirected use of statistics. All of these requirements have been fulfilled. The criteria necessary for evaluation of effectiveness of hormonal therapy were met by 944 cases, and the immaculateness of the data is such as to command the confidence of the subcommittee in the accuracy of its conclusions.

The primary purpose of this final report is to provide for the clinician a reliable orientation for his use of androgens and estrogens in the treatment of disseminated mammary carcinoma. The relative effectiveness of these two classes of sex steroids has been determined in physiologically homogeneous groups of such size as to permit statistically valid conclusions for the first time.

A concept of both basic and practical significance seems inescapable; i. e., the effectiveness of hormonal therapy is determined by some unknown biological attribute of the relationship between host and neoplasm in each patient. The nonresponsive patient, regardless of age, type of treatment or degree or sites of dissemination, had an average survival period in the narrow range of 9 to 11 months after initiation of hormonal treatment and a median survival (or 50% point) of only 7 months. Responsive patients, after beginning treatment with androgens, had an average survival of 1 months and a survival of 26 months after therapy with estrogens. In short, the demonstration of objective regression was an almost invariable signal of a less ominous course and one of greater longevity than that of the nonresponder.

Two other factors were shown to influence materially the frequency of regression, i. e., age and choice of hormone. In general, the probability of objective regression increased in rough proportion to the passage of years, both chronological and endocrinologic (postmenopausal), with two exceptions. In the fifth decade, and after the age of 80 years, the effectiveness of the androgens decreased from the level of the previous decade. In terms of endocrinologic age, the estrogens reached a plateau of effectiveness after the fourth postmenopausal year and the androgens at the eighth year after the climacteric. These disparities by age were variable in degree; the most impressive spread was noted for estrogens before and after the fourth postmenopausal year, or in the order of 15 and 38% respectively. It is notable that estrogens continued to produce objective regressions in 4 of every 10 patients throughout the remaining postmenopausal years.

Most persistent of the myths surrounding hormonal therapy is the supposed superiority of androgens for skeletal metastasis. The best that one can say for this whimsy is that only in bony deposits did the androgens approach the effectiveness of estrogens in producing healing and recalcification. In soft tissue metastasis, the use of estrogenic substances for patients more than four years beyond the climacteric was associated with rates of regression in excess of 40%, whereas androgens in a com-

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Chairman, Subcommittee on Breast and Genital Cancer, Committee on Research, Los Angeles.

able group were effective in only 18% of pa- ts. In fact, at any postmenopausal time, in any metastatic complex, estrogens invariably were equal to or, more often, exceeded androgens in effectiveness. Even in patients zero to four years postmenopausal, estrogens were not significantly inferior to androgens, with regression rates of 15 and 18%, respectively, in cases refractory to any other plan of therapy. The preferential use of estrogenic agents should increase rates of regression, over those induced by androgens, as much as twofold in postmenopausal women.

Therapeutic neglect of estrogens may, in part, be traced to the concept of "estrogen dependence" made popular by some authors. Their lack of logic is obvious in the fact that therapy with androgens is least successful in premenopausal women, when the principle of a hormonal "antagonist" should produce maximum effectiveness. The best performance of androgens in tumor suppression, on the contrary, occurs at the opposite end of the physiological scale, or at a time the patient is more than 7 years postmenopausal, when its use is accompanied by objective regression in almost 30% of patients.

Such considerations lend some support to the current preference for oophorectomy as a primary measure for palliation in genuinely disseminated disease prior to the menopause and also in the first three postmenopausal years. Although not a part of this study, this ablative approach earns approval by default over androgens, with their high rate of failures, the indignities of the induced state of virilism, and even by the occasional hazard of interconvertibility to estrogen.

Another contribution of this study to our knowledge of the natural history of mammary carcinoma concerns a relatively small fraction of the total sample, which may have a disproportionate impact on statistics of survival through an odd facet of biological behavior. This group is made up of women who had definitive treatment of their primary disease prior to the menopause and in whom a natural menopause intervened before metastatic disease became evident. For convenience, this group is referred to in these paragraphs as B7 patients. This sequence of events was attended by an inordinately long free interval, i. e., the lapse of time from primary treatment to recognition of metastatic disease. Excluding B7 cases, the average free interval for all other cases was 40.9 months, whereas for all B7 patients it was 139.7 months. Expressed in years, these values become, respectively, 3.40 years compared to 11.58 years.

There is also a tendency toward a negative correlation between the length of the free interval and the frequency of tumor regression. For example, the longest free period by far was recorded for naturally menopausal, estrogen-treated B7 patients, who enjoyed a phenomenal average of 16.6 postoperative years of freedom from disease but who were the nonresponders of this group; the responsive counterpart of such patients had an average free interval of only 6.6 years. Whatever the biological factors may be which contrive to produce so remarkable a free interval, they are without importance after metastasis is evident; the interval from initiation of hormonal therapy to death is comparable to the interval in all other postmenopausal cases.

The identification of the B7 group is of more than academic interest. In fact, it was an apparent inconsistency in certain data that led our biometric consultant to the discovery of the B7 group. The presence of relatively few B7 cases has a distortional effect on survival figures, requiring their identification and separation from even large series of cases, in the interest of more accurate data.

So complex is the biological constellation of mammary carcinoma that still other "mavericks" of peculiar natural history may yet remain for discovery by future investigators. Indeed, it is possible that the data developed in this study retain other biological oddities, requiring for their discovery only fresh minds and new approaches.

LUCANUS–APOSTLE AND PHYSICIAN

The narrative by Taylor Caldwell,[1] published last summer, "Dear and Glorious Physician," is the second historical novel about St. Luke that has appeared in recent years. Early in the preceding decade, after an intensive historical study of ancient medicine and ancient history, Frank Slaughter,[2] a physician turned novelist, presented a delightful portrayal of medical practice by St. Luke at the time of Christ. After I had read Slaughter's tale of St. Luke, I queried the author as to the source of information that might have been helpful in interpreting the reference to the treatment of gout 2,000 years ago. His reply was forthright, with the frank admission that a considerable quantity of speculation entered into the construction of this and other portions of his novel. ". . . and when Luke told him of the need of Ambassador Gallio for the powdered crocus leaves (Colchicum) which had so effectively relieved the gout for Sergius Paulus, he immediately procured a supply and took it to Gallio himself. Relief was immediate. . . ."

The recent recounting by Caldwell presents a different version of St. Luke's story that is equally interesting and not because of any particular reference to a disease entity. The volume is dedicated to her physician, Dr. Samuel A. Vogel, and his late wife, Frances Vogel, of Buffalo. There is also a credit in the preface to Dr. George E. Slotkin of Eggertsville, N. Y., for his help in interpreting ancient and modern medicine to the author.

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[2] Slaughter, F. G.: Road to Bythinia, Doubleday & Company, New York, 1951.

The title of Caldwell's book is taken from the gospel according to St. Paul: "Our most dear Physician." The only gentile among the apostles, Lucanus did not communicate directly with Christ but prepared his account for the New Testament from hearsay, from conversation with patients and friends in Asia Minor who knew Christ, and from his contacts with several of the other apostles, especially Paul. St. Luke was the most literary among the writers of the New Testament and is credited with the third gospel and the Book of Acts composed in the years 78-93 A.D. The father of St. Luke was born a Greek slave who became free some time after his son's birth. The early years of Luke's life were spent near Antioch. After his medical training, which was pursued in Alexandria, he conducted a practice that extended from Rome to Athens and into the biblical land. The custom of holding consultations, prescribing treatment, and practicing surgery over a wide geographical area was characteristic of physicians as successful and as popular as Lucanus and Hippocrates. Each one was a Greek by birth but a physician of the world by demand and desire, who made indelible imprints on ancient civilization. Luke's friendship with Paul is believed to have begun in Antioch and continued throughout the Eastern Mediterranean lands, at times as his medical attendant, at other times as a missionary with a common purpose. "Dear and Glorious Physician" is recommended reading. Since it was published several months ago, it should not be difficult to obtain a copy from your lending library. There is yet another reference to St. Luke that should be mentioned for physicians who may be in Toledo, Spain, and have an opportunity to visit the Toledo cathedral. An El Greco of St. Luke, which hangs in the Cathedral, shows him to be a slight, wistful man with a facial expression of deep dedication.

J. H. T.

INFLUENZA VACCINES

Epidemics of influenza and other viral diseases such as Eastern equine encephalomyelitis now receive great attention in mass news mediums and fire the imagination of the lay press and its readers. As more and more of the common infectious diseases come under control we learn of the fear of an unknown virus "X" which, in some minds, threatens to decimate the population in the fashion of plague. News stories and dramas describing man subjected to the whims and vagaries of nature will always sell. Since epidemics of influenza can be controlled by immunization with currently available and properly constituted influenza vaccine, it is important to prevent public hysteria by providi information about the causation and prophylaxis influenza.

In our time the medical profession has come f circle in attitudes toward influenza. The spec of the 1918 pandemic still hovers for older gene tions of practitioners who remember its terr The younger group of physicians for 40 years h experienced only the annual epidemics of a d ease often so mild that influenza was confused w severe colds or even a gastrointestinal upset. Ma authorities did not regard the illness as a gene public health hazard or even a reportable comm nicable disease. The reawakening has come duri the past three years as we learned once again t this formidable virus can rapidly spread from far corners of the earth, cause large numbers cases, occasionally produce severe pneumo markedly affect death rates, and result in the ruption of community activities. Many clinical a epidemiologic lessons were relearned during 1957-58 pandemic.

During the intervening period between the gr pandemics it had been clearly demonstrated t influenza could be prevented by immunization w specific formalin inactivated virus vaccine. It also found that classic influenza was caused by t distinctly different antigenic types, A and B, a that variants of each type successively replace p viously prevalent strains. These changes were f recognized as immunologically important w vaccines did not protect against the 1947-1948 e demics. The composition of vaccines was theref varied periodically to encompass these antige changes in viruses. Results of laboratory analy of virus isolates from the Far East early in 1 made it quite clear that another marked s among type A viruses had occurred and that a p demic of influenza probably would develop out the rapidly moving epidemics in Asia. Vacci containing the new variant were prepared a tested as soon as possible because it was kno that the older vaccines would not be effecti against the new antigenic form.

In spite of heroic effort, the goal of 60 milli doses of vaccine was not met until after the gr wave of the 1957 epidemic had passed. Nevert less, this unusual opportunity for field trials w the new vaccine was seized by many investigato The results from these several trials indicated th depending on dosage injected, the degree of p tection conferred varied from a 42 to 75% redu tion in the incidence of influenza. When small amounts of vaccine were injected intradermally subcutaneously, less protection was obtained th when a full dose (1 cc.) was administered. Of gre importance was the finding that the development serum antibody closely paralleled the degree of r sistance afforded by vaccination. A report in th issue, page 1223, by Dull and his associates de cribes such protection during the epidemic in the fall of 1957 and also notes the marked decrease in antibody levels six months after vaccination. However, when the epidemic wave of the winter of 1958 swept through the test population, vaccinated persons experienced much less influenza than did nonvaccinated subjects. Perhaps the earlier vaccination provided a degree of immunity which was rapidly boosted or enhanced during the second epidemic and thus provided resistance to overt disease.

Since vaccination is at present the only effective means known to cope with influenza epidemics, ontinuing efforts must be directed at increasing he potency of vaccine. One approach to preparedness for the advent of the next strain is to ompound a vaccine containing the widest possible ange of known influenza variants. This has been done, and the results of tests by Jensen and his olleagues with vaccines containing four or six different strains are reported on page 1230 in this ssue of THE JOURNAL. The role of dosage schedules and the incidence of prevaccination antibody n different age groups two years after the first sian epidemics have also been examined.

A tremendous body of knowledge has accumulated about Asian influenza, as shown by a recent ist containing 421 papers, reviews, and communications since 1957. What is needed now is a synthesis of wisdom from these experiences which will ead to a rational program for prevention of influenza. The United States Public Health Service and he World Health Organization are aware of their esponsibilities in this area. Several different research programs have been sponsored by the Public Health Service, and recently an opportunity for the evelopment of new viewpoints and discussion of roblems was provided at the International Conference on Asian Influenza held in Washington at the National Institutes of Health, February 17-19, 1960. The consensus is that influenza will continue to cause epidemics and that new variants will arise periodically through a mechanism which is as yet not understood. An elaborate system of laboratories and epidemic surveillance has been arranged to provide intelligence as soon as possible for each epidemic. The Asian variant can be expected to prevail for several more years before being replaced by a different type A virus.

The United States Public Health Service has recommended influenza vaccine for the following groups: (1) persons for whom the onset of influenza might represent an added health risk, such as those with cardiovascular or pulmonary conditions, those over 55 years of age with chronic illness of any type, and pregnant women; (2) persons responsible for the care of the sick; (3) persons responsible for providing such essential public services as law enforcement, fire protection, transportation, and communication; and (4) industries and other commercial enterprises that wish to keep the employee absenteeism rate from rising. Many authorities point out that the homemaker must be protected also in order to preserve the well-being of the family unit.

Because the attack rate is highest in children and young adults, use of vaccine in these age groups will be most efficacious. Since severity and extent of an epidemic cannot be predicted accurately, annual vaccination is recommended for all age groups.

GROWING NEED FOR TEEN-AGE CLINICS

Since the first teen-age clinic was established in Boston in 1952 there has been an increasing awareness of the special health and psychological problems of teen-agers. Dr. Arthur Roth,[1] a pioneer in this poorly understood field, has written a medical guide for young people and their parents that should help clarify many of the problems of teen-agers which although common are perplexing to those who experience them. The most baffling paradox to the growing child is normal variation. Marked differences in height, weight, age of onset of puberty, and development of secondary sex characteristics can appear as frightening abnormalities to young persons and are not always understood by their parents. These and other considerations are dealt with in the teen-age clinics and are described in the guide. The manner in which these problems are handled can be an important factor in determining the attitude taken toward the medical profession in subsequent years by today's teen-agers.

The busy practitioner who sees patients of all ages would do well to take stock of his usual approach to teen-agers. They are no longer children and not yet adults. The mere fact of being a teen-ager is not, as some persons seem to believe, an illness, and the term teen-ager is not synonymous with juvenile delinquent or "crazy mixed-up kid." No one, least of all Dr. Roth, believes that all teen-agers could or should be treated in a special clinic, although this may be desirable in some cases. On the contrary he believes that these patients must be treated with a heartfelt sympathy and kindly understanding that they sometimes are unable to find either at home or in the general medical clinic. There is probably no more rewarding experience in medicine than that of helping these youngsters to a better understanding of themselves. Dr. Roth concludes his guide on a note of optimism. Underneath the faltering and stumbling of the teen-ager he recognizes a hard core of human value that augurs well for the future of the nation and of the world.

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1. Roth, A.: The Teen-Age Years: A Medical Guide for Young People and Their Parents, Garden City, New York, Doubleday & Company, Inc., 1960.

ORGANIZATION SECTION

DR. NORWOOD TO DIRECT SPECIAL STUDY COMMITTEE

The American Medical Association has established a scholarship program for medical students. A special study committee was appointed to direct the program. William F. Norwood, Ph.D., chairman of the division of legal and cultural medicine, College of Medical Evangelists, Los Angeles, was named staff director of the committee. From 1950 to 1951 he served as a staff associate in a survey of medical education sponsored by the A. M. A. and the Association of American Medical Colleges.

Last December the House of Delegates of the A. M. A. adopted a resolution that a scholarship fund be established to aid deserving students to enter the field of medicine and that the fund be backed by the A. M. A. as a primary sponsor. Dr. L. S. McKittrick, Brookline, Mass., who is chairman of the Council on Medical Education and Hospitals, will serve as chairman of the committee.

DR. SCHOENFELD JOINS COUNCIL STAFF

The Council on Medical Education and Hospitals has added a new member to its field representatives who review intern and residency programs. He is Dr. Herbert H. Schoenfeld of Washington, D. C. Dr. Schoenfeld has served the Council as a regional evaluator for graduate programs in surgery. A graduate of George Washington University School of Medicine, he is retiring as assistant clinical professor of surgery at his alma mater. Formerly he was on the consulting staff of the Washington Medical Center and the senior advisory staff of the Children's Hospital in Washington.

GOVERNMENT SERVICES

NAVY

Recognition and Treatment of Diving Casualties.—A two-week active duty training course in recognition and treatment of diving casualties will convene at the U. S. Naval School of Deep-Sea Divers, U. S. Naval Weapons Plant, Washington, D. C., on July 18. This course offers didactic training in underwater physiology and in the recognition and treatment of casualties associated with any kind of diving. Although this course is given for active duty personnel en route to stations where there is some diving activity, vacancies in the course may be filled by reservists on active duty for training. Inactive Naval Reserve medical officers are eligible to attend. All continental naval districts have been allocated quotas.

Change of Duties.—Capt. Henry C. Hunley Jr., M. C., was made deputy director of the aviation medicine operations division of the bureau of medicine and surgery in February. He was formerly on duty at the Marine Corps Air Station, Quantico, Va.—Capt. Robert E. Walsh, M. C., reported to the bureau of medicine and surgery in February for duty as head of the procurement branch of the physical qualifications and medical records division. He was formerly assigned to the staff of the Naval Hospital, Camp Pendleton, Calif—Capt. Sidney D. Bond Jr., M. C., recently reported to the bureau of medicine and surgery for duty as head of the Medical Corps training section. His former duty assignment was on the staff of the U. S. Naval Hospital, Camp Lejeune, N. C.

PUBLIC HEALTH SERVICE

Russian Visitors.—In February, four Soviet biochemists began a month's survey of United States research developments in metabolic diseases. They spent three days at the National Institutes of Health before visiting research centers throughout the country. Dr. G. Gilbert Ashwell, of the National Institute of Arthritis and Metabolic Diseases, served as the group's director on the entire trip. Members of the Russian group are Drs. Grachiya K. Bunyatyan, of the Armenian Academy of Sciences; Mikhail P. Chernikov, of the Institute of Biology and Medical Chemistry, U. S. S. R. Academy of Sciences, Moscow; Nikolai N. Demin, of the U. S. S. R. Academy of Sciences, Moscow; and Ilya I. Ivanov, of the Leningrad Pediatrics Medical Institute. The Soviet scientists came here under provisions of a 1958 agreement between the United States and the Union of Soviet Socialist Republics to exchange missions in various fields. A return mission of U. S. scientists, headed by Dr. Floyd S. Daft, director of the National Institute of Arthritis and Metabolic Diseases, will go to the U. S. S. R. in September.

MEDICAL NEWS

ALASKA

Human Brucellosis Cases.—The Alaska Division of Health announced that two cases of human brucellosis were reported to the division during the past year. In both cases raw caribou meat or bone marrow were believed the source of infection. One case was a 13-year-old Eskimo girl from Wainwright and the other an 18-year-old girl from Barrow. Investigations of the cases were carried out by the U. S. Public Health Service personnel. Since 1939 only 51 cases of human brucellosis have been reported in Alaska, 25 of which occurred in 1942 in a community in the interior and were attributed to consumption of improperly pasteurized milk.

ARIZONA

Hospital Lecture.—"Day and Night Hospital—An Advance in the Management of Psychiatric Patients" was the topic of a talk given at Camelback Hospital, Phoenix, Feb. 23 by Dr. John Gussen, Los Angeles. Dr. Gussen spoke to the members of the Maricopa County Medical Society who were invited to attend the regular Tuesday morning staff breakfast by Dr. Otto L. Bendheim, medical director of the hospital. Dr. Gussen served as chief of the Day-Night Hospital, Langley Porter Neuropsychiatric Institute, San Francisco, and was assistant professor of psychiatry at the University of California School of Medicine, San Francisco, before his appointment as director of psychiatry at Cedars of Lebanon Hospital in Los Angeles.

COLORADO

Institute on Alcoholism in Boulder.—The University of Colorado campus will be the setting for the first Colorado Institute on Alcoholism, sponsored by the Colorado Commission on Alcoholism, the CU Extension Division, and the CU School of Nursing, June 26-29. Programs of general interest will be arranged for educators, clergymen, probation, parole, and correctional officers, personnel directors, police officers, and community leaders. There will be professional workshops for nurses, social workers, and rehabilitation personnel. Among the specialists who will lecture will be Dr. Marvin A. Block, of Buffalo, N. Y., chairman of the Committee on Alcoholism, American Medical Association, and Mrs. Marty Mann, of New York City, executive director, National Council on Alcoholism.

DISTRICT OF COLUMBIA

Freedmen Alumni Establish Two Awards.—Awards honoring the memory of two pioneer Freedmen's Hospital physicians—Dr. Daniel Hale Williams and Dr. William Alonza Warfield—were established by the Association of Former Internes and Residents of Freedmen's Hospital. First award will be presented at the 38th annual meeting of the association at the Howard University College of Medicine, Jan. 7-9. The Daniel Hale Williams Award will be given annually to an intern or resident of the hospital for "outstanding achievement" during the current year. The William Alonza Warfield Award will be given annually to a former intern or resident of the hospital for "distinguished achievement in the field of medicine and surgery and allied specialties, or for distinguished achievement in the national, civic, or community, or patriotic welfare." Dr. Williams was a charter member of the American College of Surgeons and a founder of Providence Hospital, Chicago (1891). Dr. Warfield served as surgeon-in-chief of Freedmen's Hospital for 35 years (1901-1936). The present hospital structure was erected during his administration, in 1908. A founder and first president of the association, organized in Newark, N. J., in 1919, Dr. Warfield later served as honorary president and honorary president emeritus on retirement from the hospital. Dr. Williams died in 1931, Dr. Warfield in 1951.

ILLINOIS

Dr. Fatherree to Head State Health Department.—Dr. Leroy L. Fatherree, director of the Champaign-Urbana District Health Department, was appointed director of the Illinois Department of Public Health by Governor William G. Stratton, effective Feb. 1. Dr. Roger F. Sondag, of Murphysboro, was appointed assistant director. In 1939 Dr. Fatherree organized the Little Rock, Ark., public health department and served there until 1945. In 1947 he reorganized the Omaha public health department to combine it with the department of Douglas County, Neb. Before coming to Champaign-Urbana, Dr. Fatherree headed the Will County Public Health Department. He is president of the Ameri-

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

can Association of Public Health Physicians and is a member of the governing board of the American Public Health Association.

Chicago

Hospital Plans Expansion.—Rest Haven Rehabilitation Hospital has launched a campaign for funds to build a new wing for patient services. The estimated cost of the new construction is one million dollars. Founded in 1912, Rest Haven Rehabilitation Hospital is a specialized institution which treats patients with such conditions as strokes, amputations, arthritis, paralysis, and cardiac disease. Building funds are being provided by the federal government under the Hill-Burton Act, the Ford Foundation, and the Jewish Federation of Metropolitan Chicago, of which Rest Haven Rehabilitation Hospital is an affiliate.

Society News.—At the annual meeting of the Chicago Dermatological Society Jan. 20 the following officers were elected: president, Dr. I. Myron Felsher; vice-president, Dr. Allan L. Lorincz; and secretary-treasurer, Dr. Frederick J. Szymanski.—— At the annual meeting of the Chicago Diabetes Association Feb. 5, the following officers were reelected for terms expiring in February, 1961: Drs. James B. Hurd, president; M. David Allweiss, first vice-president; R. Lincoln Kesler, second vice-president; Ralph E. Dolkart, secretary; and Mr. Melvin C. Holmes, treasurer.

KENTUCKY

Heart Operation Recorded on Video Tape.—On Jan. 29, an open heart operation was performed at the Louisville Children's Hospital on a 5-year-old boy for the correction of a large interatrial septal defect by a team from the faculty of the University of Louisville Medical School. The entire operation was recorded on video tape by WHAS-TV. On the evening of Feb. 24, WHAS-TV devoted an hour and a half to a broadcast of the operation as taped. The close-up details of the procedure were photographed through a mirror over the operating table. The result was technically excellent. During the showing on television the two operating surgeons *(in the studio)* made appropriate commentaries. The actual broadcast was preceded by a 15-minute program in which the operating room and its equipment, including the heart-lung apparatus and pump, were demonstrated. It was followed by a regularly scheduled half-hour program entitled "What's Your Question?" in which the two doctors answered questions which were telephoned in by viewers. The surgeons were Dr. J. Alex Haller and Dr. William F. Rubel, of Louisville. The broadcast was sponsored jointly by the Medical School and the Kentucky and Jefferson County Heart Associations.

MARYLAND

Annual Meeting in Baltimore.—The Medical an Chirurgical Faculty of the State of Maryland wi hold its annual meeting April 20-22 at the Alcaza Baltimore. Dr. Willis J. Potts, of Chicago, wi present "Congenital Anomalies of the Esophagu as the I. Ridgeway Trimble Lecture, the afternoo of April 20. The program includes the followin papers:

Biological Effects and Hazards of Ionizing Radiation, D Russell H. Morgan, Baltimore, Dr. Donald R. Chadwic Washington, D. C., Richard H. Chamberlain, Philade phia, and Dr. William B. Looney, Baltimore.

Chemosurgery of the Basal Ganglia in Parkinsonism, Dy tonia Musculorum Deformans and Multiple Sclerosis, D Irving S. Cooper, New York City.

Atypical Variants of Viral Hepatitis, Dr. Gerald Klatski New Haven, Conn.

Histaminic Cephalgia; Differential Diagnosis and Treatmen Dr. Bayard T. Horton, Rochester, N. Y.

Stein-Leventhal Syndrome (Polycystic Ovary Syndrome Dr. Robert B. Greenblatt, Augusta, Ga.

Immunization for Young and Old, Dr. Joseph E. Smad Washington, D. C.

The J. M. T. Finney Fund Lecture will be give the morning of April 21 by Lt. General Leona D. Heaton, Surgeon General, U. S. Army. Ps chiatric and hypertension panel discussions a planned, and a clinical pathological conference scheduled. The presidential dinner will be hel April 21. For information, write Dr. William (Ebeling III, 1211 Cathedral St., Baltimore 1.

MASSACHUSETTS

Fellowship in Cancer Chemotherapy.—A cance chemotherapy fellowship has been established i the medical services of the Lemuel Shattuck Hospital in cooperation with the Warren Laboratorie of the Collis P. Huntington Memorial Hospital c Harvard University at Massachusetts General Hospital, Boston. The program will consist of trainin in the use and critical evaluation of new chemotherapeutic agents in man and animals, with opportunities for individual research. Fellows should hav prior training in internal medicine. Informatio may be obtained from the Oncology Division, Medical Services, Lemuel Shattuck Hospital, Boston 30

MICHIGAN

Institute on Chronic Disease Control.—An Institut on Chronic Disease Control will be held June 13-2 at the University of Michigan School of Publi Health, Ann Arbor. Co-sponsors with the school ar the Directors of Chronic Disease Teaching Programs of Schools of Public Health, the Associatio of State and Territorial Chronic Disease Program Directors, the Michigan Department of Health, and the U. S. Public Health Service. The program will include lectures, seminars, and discussions in the following areas: health promotion, prevention, early detection, multiple screening, home care, institutional care, and rehabilitation, in relation to such chronic diseases as heart disease, cancer, diabetes, glaucoma, and cerebral vascular disease. The institute is designed primarily for public health physicians concerned with chronic disease control programs, but selected public health nurse consultants, nutritionists, and health educators concerned with the planning and administration of chronic disease programs at state and local levels will be eligible to attend. Application for participation must be received not later than May 15. Information may be obtained by writing the Director of Continued Education, School of Public Health, University of Michigan, Ann Arbor, Mich.

NEW HAMPSHIRE

Research Conferences.—The Gordon Research Conferences for 1960 will be held from June 13 to Sept. 2 at Colby Junior College, New London, New Hampton School, New Hampton, and Kimball Union Academy, Meriden. The conferences were established to stimulate research in universities, research foundations, and industrial laboratories by an informal type of meeting consisting of scheduled lectures and discussion groups. Time is available for informal discussions. Meetings are held in the morning and evening, Monday through Friday (except Friday evening). Afternoons are available for recreation, reading, or participation in discussion groups. The purpose of the program is to bring experts up to date on the latest developments, to analyze the significance of these developments, to provoke suggestions concerning the underlying theories and profitable methods of approach for making progress. Attendance is by application, which must be submitted on the standard application form obtainable from W. George Parks, Department of Chemistry, University of Rhode Island, Kingston, R. I. Attendance at each conference is limited to about 100 conferees.

NEW YORK

British Surgeon Named Department Chairman.—Dr. Charles G. Rob, professor of surgery at the University of London since 1950, will become chairman of the University of Rochester department of surgery in July. He will succeed Dr. W. J. Merle Scott, who has held that position since 1953. Dr. Scott is retiring June 30. Dr. Rob has been visiting surgeon-in-chief at Peter Bent Brigham Hospital in Boston and Presbyterian Hospital in New York City, and last fall was visiting professor of surgery at the University of California at Los Angeles. He also received some of his medical training at McGill University Medical School in Montreal, serving a residency at the Royal Victoria Hospital in that city. In 1954, he reportedly was the first surgeon to successfully reconstruct the carotid artery. Dr. Rob was elected last summer as president of the International Society for Cardiovascular Surgery.

New York City

Unit for Cardiac Diagnosis.—Children with heart disease will be studied from infancy through adolescence at New York University–Bellevue Medical Center in a new cardiac diagnostic unit for which plans have been completed. This unit is being created as a memorial, by colleagues and friends, to the late Dr. Janet S. Baldwin, associate professor of pediatrics at the medical center and a pioneer in the diagnosis of congenital cardiac anomalies in children. Dr. Eugenie A. F. Doyle, director of the Children's and Adolescent Cardiac Service, announced that the new unit will include facilities for cardiac catheterization and cine angiocardiography and will be under the direction of Dr. Edmund H. Reppert Jr., assistant professor of clinical medicine at the medical school. The new unit will start functioning about May 1.

Dr. Lanman Named Department Chairman.—Dr. Jonathan T. Lanman, associate professor of pediatrics, New York University College of Medicine, was appointed professor and chairman of the department of pediatrics at the State University of New York Downstate Medical Center and chief of pediatrics at the Kings County Hospital Center, Brooklyn. Dr. Lanman will take over his new duties April 1, succeeding Dr. Richard L. Day, who resigned the two positions to become medical director of Children's Hospital of Pittsburgh and chairman, department of pediatrics, University of Pittsburgh School of Medicine. Dr. Lanman served as a United States Public Health Service Fellow at the University of California from 1946 to 1949, when he became instructor in pediatrics at New York University College of Medicine.

Hospital News.—The Swedish Hospital, Bedford Ave. and Dean St., announced the opening of a department of angiology. The inpatient service is in charge of Dr. Saul S. Samuels and is prepared to admit cases of peripheral gangrene and chronic leg ulcers. The outpatient clinic is under the direction of Dr. Herbert E. Shaftel and Dr. Samuels, and will admit ambulatory cases of peripheral arterial disease on Tuesdays at 10 a. m.——Dr. Donald V. Cooney, Garden City, L. I., recently director of professional services at Pittsburgh Veterans Administration Hospital, has been named director of the new prehospitalization home care program at the Jewish Chronic Disease Hospital, Brooklyn. The program is a five-year study made possible by the National Institutes of Health to determine the feasibility of treatment of victims of stroke at home.

NORTH CAROLINA

Plan Reopening of Children's Center.—Dean C. C. Carpenter, Bowman Gray School of Medicine, Winston-Salem, announced long-range plans for the reopening of the Graylyn Estate as a center for exceptional children. Graylyn, which until one year ago was the adult psychiatry unit of Bowman Gray School of Medicine of Wake Forest College, will offer its facilities in the field of emotional and neurological problems confronting children. The program is under the direction of Mr. Joseph R. Grassi, assistant professor of psychology at Bowman Gray and director of the Medical School's Psychology, Reading and Speech Center at Reynolda. The program will be coordinated with the teaching program of the city and county schools, and Western Carolina College, and will provide classes for trainable retarded children, sheltered workshop training for educable retarded children on a part-time basis, a summer program for gifted children, training classes for teachers of emotionally disturbed children, and a psychological clinic.

The Graylyn Estate.

OHIO

Drs. Warren and Hackett Named Surgeons Emeriti.—The honorary title of surgeon emeritus was conferred on Dr. George S. Hackett and Dr. Archie W. Warren recently by representatives of Mercy and Timken Mercy hospitals, Canton. Both physicians, who retired recently from active practice, received plaques from the two hospitals "commending them for their decades of outstanding hospital and medical services."

Dr. Sabin Honored by Alma Mater.—Dr. Albert B. Sabin received the 1960 Medical Alumni Award from New York University "for his outstanding medical statesmanship." He is a 1931 graduate of NYU College of Medicine. The honor was conferred Feb. 22 in New York City. Dr. Sabin, developer of a live-virus poliomyelitis vaccine, recently announced he will turn to cancer research in 1961. He is professor of research pediatrics at the University of Cincinnati College of Medicine and fellow in Cincinnati Children's Hospital Research Foundation. Dr. Sabin's "distinction as a scientist" prompted his selection, the NYU administration said. Dr Sabin received an honorary doctor of science degree from NYU in June, 1959.

OKLAHOMA

Break Ground for Research Building.—Groundbreaking ceremonies for the University of Oklahoma Medical Research Building were held Jan. under joint sponsorship of the center and th Oklahoma City Chamber of Commerce. Paul A Weiss, Ph.D., head of the Laboratory of Developmental Biology at the Rockefeller Institute fo Medical Research, New York City, was principa speaker. The building, to cost about $800,000, i being constructed on the south side of NE 13 Stree in front of University Hospital and to the west o the hospital's outpatient clinics wing. The fou story structure will house some 50 laboratories an related facilities. Construction of the laborator space for faculty members was made possible by $400,000 federal health research facilities gran awarded in 1957 and matched by a $400,000 appropriation of the 1959 state legislature.

GENERAL

1960 Census.—The 1960 Population Census will b conducted April 1. Every fourth household will b asked to answer the question, "What kind of wor was he doing?" for each person 14 years of age o older. In order that the occupation statistics on th medical profession be developed as accurately a possible, the Census Bureau has asked that we pas along to our readers a reminder that this questio on occupation should be answered completely an precisely. In many cases the entry should consist o at least two words. Some examples of acceptabl entries are: clinical pathologist, gynecologist, medical doctor, ophthalmologist, orthopedic surgeon pediatrician. Please note that the word "doctor" b itself is not an adequate entry.

Plastic Surgeons Meeting.—The spring meeting o the American Society of Facial Plastic Surgery wil be held Wednesday, April 6, at the Hotel Elysee 60 E. 54th St., New York City. A business meeting is planned for 5:30 p. m. at which the election o officers will take place. The scientific program wil consider "Methods of Otoplasty" and the following persons will participate: Drs. Oscar J. Becker Chicago; Richard T. Farrior, Tampa, Fla.; William Schwartz, Passaic, N. J.; Herbert Friedman, Brooklyn; Samuel M. Bloom, New York City; and Sidney S. Feuerstein, New York City. Dr. Feuerstein will present a motion picture. For information, write the American Society of Facial Plastic Surgery 123 E. 83rd St., New York 28.

Survey of Snake-Bite Incidence.—The New York Herpetological Society is conducting a survey on the incidence, causes, and treatment of snake-bite in the continental United States. The society asks that hospitals and physicians responding to the treatment of snake-bite victims volunteer the following information: victim's initials, sex, age, height, weight, type and/or species of snake, preliminary treatment and antivenin treatment (dosage and frequency of doses), complications, and result of treatment. The exact length of convalescence, if known, would be appreciated. The data will be recorded and tabulated by John Hauser of Philadelphia and then evaluated. Free copies of the report will be sent to all hospitals and physicians taking part in the survey. The survey will cover the period Dec. 31, 1957, through Dec. 31, 1959. All reports should be sent to the Director of Research, New York Herpetological Society, Box 71, Brooklyn 9, N. Y.

Meeting on History of Medicine.—The 33rd annual meeting of the American Association for the History of Medicine will be held March 24-26 in Charleston, S. C., with headquarters at the Francis Marion Hotel. Ludwig Edelstein, Ph.D., of Baltimore, will present the Garrison Lecture, "The Distinctive Hellenism of Greek Medicine," the evening of March 24. A symposium on primitive medicine will include the following papers:

Foundations of Ancient Mesopotamian Medicine, Martin Levey, Ph.D., Princeton, N. J.
Origin of Death, Warner Muensterberger, Ph.D., Brooklyn.
Relationship Between Folk and Scientific Medical Practice in a Peasant Community, Michael Horowitz, Ph.D., Kent, Ohio.

Speaker at the annual dinner March 25, 7:30 p. m., will be Mr. Samuel Gaillard Stoney, of Charleston, S. C. For information, write John B. Blake, Ph.D., Secretary-Treasurer, American Association for the History of Medicine, Smithsonian Institution, Washington 25, D. C.

New Journal of Psychiatry.—Founded as a forum for American and international psychiatry, *Comprehensive Psychaitry* will be published bimonthly, the first issue being January-February, 1960. The journal will be devoted to the publication of articles concerning clinical psychiatry, research, therapeutic practice and psychiatric training. The first issue will feature papers on pharmacotherapies, existential analysis, direct analysis, research, psychiatric training, clinical psychiatry, and therapeutic practice. It is planned that at least once a year an entire issue will be reserved for exploration and discussion of one specific theme of universal interest. The journal is edited by Dr. Fritz A. Freyhan, clinical director and director of research, Delaware State Hospital. Chairman of the editorial board is Dr. Paul H. Hoch, New York City. The international advisory board has 12 members. The price for six issues is $8 per calendar year. Single issues are $2. For information, write Comprehensive Psychiatry, Grune & Stratton, Inc., 381 Park Avenue South, New York 16.

Meeting of Obstetricians and Gynecologists.—The American College of Obstetricians and Gynecologists will hold its eighth annual meeting at the Netherland Hilton Hotel, Cincinnati, April 3-6. The scientific program on Monday, Tuesday, and Wednesday, will consist of the presentation of papers, correlated seminars, clinical and breakfast conferences, and motion pictures. More than 240 participants are included in the program. Each seminar will consist of four sessions spread over three days, all devoted to the same subject under the same leader. A "doctor's luncheon" will be given on Monday. On Tuesday morning, a panel discussion on medical service plans, with representatives of industry, labor, insurance, and medicine speaking on third-party plans and their impact on obstetrics and gynecology, will be moderated by Dr. Donald C. Harrington, Stockton, Calif. For information, write Mr. Donald F. Richardson, Executive Secretary, The American College of Obstetricians and Gynecologists, 79 W. Monroe St., Chicago 3.

Orthopedic Meeting in Wichita.—The 1960 meeting of the Mid-Central States Orthopaedic Society will be held April 8-9 at the Lassen Hotel and the Kansas Gas & Electric Company Building, Wichita, Kan. Six papers include case presentations. Other papers scheduled on the program are as follows:

End-Result Studies of Forearm Fractures Reduced with Mal-Alignment in Children, Dr. Ward A. McClanahan, Wichita.
Multiple Pin Fixation of Femoral Neck Fractures, Dr. Spencer C. McCrae, Salina, Kan.
Traumatic Subtalar Dislocation, Dr. John F. Thurlow, Hays, Kans.
Bone Stimulation Procedures in Children, Dr. Harry G. Kroll, Topeka, Kan.
Heyman Procedure for Adducted Forefeet, Dr. Henry O. Marsh, Wichita.
The Use of Plaster of Paris to Fill Defects in Bone, Dr. Leonard F. Peltier, Kansas City.
Fractures About the Knee Treated with Internal Fixation with Immediate Mobilization, Dr. Charles R. Rombold, Wichita.
End-Result of Mitchell Procedure for Bunions, Dr. Harry O. Anderson, Wichita.

A panel discussion with case presentations will precede the business meeting April 9. For information, write the Mid-Central States Orthopaedic Society, 3244 E. Douglas, Wichita 8, Kan.

Annual Gastroscopic Meeting.—The 19th annual meeting of the American Gastroscopic Society will be held Wednesday, March 30, at the Auditorium of the Louisiana State University Medical School, New Orleans. A scientific program is arranged in three symposiums with the following titles and moderators: Nonsurgical Management of Esophageal Disease, Dr. John T. Howard, Baltimore; Endoscopic Biopsy and Exfoliative Cytology in the Diagnosis of Gastrointestinal Disorders: Techniques and Evaluation, Dr. J. Edward Berk, Detroit; Gastric Color Photography, Dr. Harry L. Segal, Rochester, N. Y. A total of eight papers will be presented at the three symposiums as follows:

The Medical Treatment of Hiatal Hernia, Esophagitis, Esophageal Ulcer and Diffuse Spasm of the Esophagus, Drs. Asher Winkelstein, New York City, and John Tilden Howard, Baltimore.
Treatment of Benign Stenoses of the Esophagus, Dr. Edward B. Benedict, Boston.
The Treatment of Cardiospasm, Dr. Regis A. Wolff, Pittsburg.
Biopsy of the Esophagus and Stomach, Dr. Eddy D. Palmer, Houston, Texas.
Biopsy of the Small Intestine, Dr. Cyrus E. Rubin, Seattle.
The Application of Exfoliative Cytology to Benign and Malignant Diseases of the Gastrointestinal Tract, Dr. Howard F. Raskin, Chicago.
A Comparison of Electronic Flash and Tungsten Light Gastroscopic Color Photography, Dr. Robert S. Nelson, Houston.
Further Experience with Gastric Color Photography, Dr. Ivan C. Keever, Chicago.

A business meeting will conclude the program. For information, write Dr. Arthur M. Olsen, 200 First St. S. W., Rochester, Minn.

Regional Meeting of Physicians in Salt Lake City.—The American College of Physicians will hold a regional meeting for Utah and Idaho Saturday, March 19, in the Little Theatre Union Building, University of Utah, Salt Lake City. Dr. Fuller B. Bailey, regent of the college, will open the meeting with an address. Thomas F. Dougherty, Ph.D., head, department of anatomy, University of Utah College of Medicine, will present "The Control of the Inflammatory Response" at the luncheon meeting. The following papers include invited authors:

Sub-Acute Thyroiditis, Dr. Lynn H. Anderson, Blackfoot, Idaho.
Recent Developments in Bilirubin Metabolism, Dr. Edwin Englert Jr., Salt Lake City.
I^{131} In the Diagnosis and Treatment of Disease, Dr. Philip R. Frederick, Salt Lake City.
The Digital Computer—A Potential Aid to Medical Diagnosis, Dr. Alan F. Toronto, Salt Lake City.
The Amino Oxidase Inhibitors and Their Role in Geriatric Medicine (Report on a 50 Patient Study), Dr. Everett J. Carmody, San Diego, Calif.
Demonstration of Cancer Cells in Peripheral Venous Blood, Samples and Significance, Dr. Cyril D. Fullmer, Salt Lake City.
Laboratory Aspects of Auto-Immune Disease, Dr. Crichton McNeil, Salt Lake City.
The Intracavitary Use of Radio Isotopes in the Medical Management of Cancer, Dr. Richard Y. Card, Salt Lake City.
Recent Clinical and Experimental Observations Concerning Diabetes Insipidus, Dr. J. Floyd Cannon, and Dr. Roy O. Schaub, Salt Lake City.

Dr. Thomas A. Findley, regent of the college, will present "The Kidney as a Metabolic Organ" at the afternoon session and will give "The Importance of Unlearning" at the banquet, 7:30 p. m., at which Dr. Theodore C. Bauerlein, governor for Utah, will serve as toastmaster.

1960 Pharmacopeial Convention.—The decennial meeting of the United States Pharmacopeial Convention will be conducted by the officers elected in 1950 who have held office during the decade when the meeting convenes in Washington, D. C., on March 29. At "full strength," the convention will consist of about 300 persons, the majority of whom will be delegates from organizations entitled to representation, including accredited colleges of medicine and pharmacy, state and national medical and pharmaceutical societies, several units of the federal government, and a limited number of organizations closely related to pharmacy and medicine. The first business of the convention will be consideration of an important revision of the present Constitution which will make it possible to seat a delegate from the newly formed Pharmaceutical Manufacturers Association. The convention will be asked to consider problems that have arisen during the past decade in the course of revising two editions of the Pharmacopeia. A function of the convention is to elect officers, a board of trustees, and a committee of revision of 60 experts to serve during the next decade. On the evening of March 28, an informal meeting is planned which will be addressed by Linwood F. Tice, Ds.C., Philadelphia, and Dr. Windsor C. Cutting, Stanford, Calif., of the present Committee of Revision, and George P. Larrick, Commissioner of Food and Drugs, Washington, D. C. During the convention, Arthur S. Flemming, Secretary of Health, Education, and Welfare, will deliver an address, as will Howard C. Newton, Ph.B., Boston, president, American Pharmaceutical Association. The present officers of the convention include Drs. Allen H. Bunce, Atlanta, Ga., president; Theodore G. Klumpp, New York City, vice-president; W. Paul Briggs, Sc.D., Washington, D. C., treasurer; and Adley B. Nichols, Ds.C., New York City, secretary. George D. Beal, Ph.D., Pittsburgh, is chairman of the board of trustees.

LATIN AMERICA

International Gastroenterology Meeting.—The second biennial scientific meeting of the Bockus Alumni International Society of Gastroenterology will be held during the week before the seventh Pan American Congress of Gastroenterology. The meeting will take place in Rio de Janeiro, Brazil, Oct. 17-21. The Brazilian host alumni will present a program, "Gastroenterology in Tropical Medicine." Alumni members are invited to present papers on

"Diseases of the Pancreas." A panel discussion will be moderated by Dr. Henry L. Bockus, Philadelphia, for whom the society is named. Free papers will be limited to 10 minutes and will be accepted until Aug. 1 on notification of the secretary general. For information, write Dr. Figueiredo Mendes, Av. Rio Branco, 257-18, Rio de Janeiro, Brazil, or Dr. James L. D. Roth, Graduate Hospital, Rm. 520, Philadelphia 46.

FOREIGN

Congress of Endocrinology in Copenhagen.—The first International Congress of Endocrinology will be held at the Technical University of Denmark, Copenhagen, July 18-23, under the presidency of Prof. Bernardo A. Houssay, Argentina. Ten symposiums at which invited speakers will participate are listed as follows:

Central Nervous System Regulation of Anterior Pituitary Secretion.
Polypeptide Anterior Pituitary Hormones.
Posterior Lobe Pituitary Hormones.
Parathyroid Hormone and Calcium Metabolism.
Aspects of Reproduction.
Adrenocortical Syndromes.
Aldosterone.
Steroid Pharmacology.
Hormone Action at the Cellular Level.
Topics in Comparative Endocrinology.

A round-table discussion on hormone assays of clinical value is scheduled. Scientific and technical exhibits and a program of social activities are arranged. For information, write the General Secretary, Prof. F. T. C. Prunty, Department of Chemical Pathology, St. Thomas's Hospital, Medical School, London S. E. 1.

Tour to Europe and Israel.—A special chartered jet-flight tour to Europe and Israel, highlighted by the dedication of the new medical school building of the Hebrew University of Jerusalem Aug. 3, was announced by the American Jewish Physicians' Committee, the medical section of the American Friends of the Hebrew University. Featuring a 12-day visit to Paris, Florence, and Rome and a two-week stay in Israel, the tour will include a seminar on Israel medicine and progress of medical research Aug. 4 at the Hebrew University's medical school. Participating physicians will be invited to attend lectures. The new medical school building of the Hebrew University, which replaces the old school premises on Mount Scopus, is the result of a five-year program and an expenditure of 5 million dollars. Funds for its construction have been raised by the 20 chapters of the American Jewish Physicians' Committee. Reservations and information for the tour may be obtained from the mid-west office of the American Jewish Physicians' Committee, 188 W. Randolph St., Chicago (FRanklin 2-5496).

Pediatric Congress in Czechoslovakia.—Dr. V. Kafka, president of the Congress Committee of the Medical Society of Czechoslovakia, Section of Pediatric Surgery, announced that the sixth annual meeting of Czechoslovak surgeons will be held in Prague, May 23-25. The program will include two main topics: Surgery of the Intrathoracic Organs and Internal Injuries, with the following subjects listed:

Open Heart Surgery.
Problems of Diagnosis and Results of Treatment in Atresia of Esophagus.
Mediastinal Tumors.
Urgent Thoracic Surgery in the Newborn and Infants.
The Importance and Value of Prevention in Traumatology.
Discussion on Injuries of CNS.
Rupture of the Heart.
Traumatic Rupture of the Tracheobronchial Tree and Lungs.
Posttraumatic Hydrocephalus.
Total Abruption of the Renal Hilus.

The official languages of the congress will be Russian, English, Czechoslovakian, and Slovak, with the lectures preferably given in English or Russian. A social program is planned, including the International Music Festival. For information, write Dr. Emil Frynta, Department of Pediatric Surgery, Charles University, Prague 2, Ke Karlovu 2, Czechoslovakia.

CORRECTION

Dr. Rosenman Is Not Dead.—In the Feb. 13 issue of The Journal, page 724, under Deaths, an obituary appeared on Dr. Jacob Daniel Rosenman. Dr. Rosenman, who resides in Venice, Calif., is not dead.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, June 21-22 and Sept. 7-8. Part II, Various Cities, April 26-27. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 21-23. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

ALASKA:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

ARKANSAS:* *Examination and Reciprocity.* Little Rock, June 9-10 Sec., Dr. Joe Verser, Harrisburg.

California: *Written.* San Francisco, June 20-23; Los Angeles, Aug. 22-25 and Sacramento, Oct. 17-20. *Oral and Clinical.* Los Angeles, San Francisco, June 19; Los Angeles, Aug. 21, and Los Angeles, Nov. 29. *Oral for Reciprocity Applicants.* San Francisco, June 18; Los Angeles, Aug. 20 and Nov. 19. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

Canal Zone: On Application. Acting Sec., Dr. B. K. Levin, Health Bureau, Balboa Heights.

Colorado:* *Reciprocity.* Denver, April 12. *Examination.* Denver, June 14-15. Sec., Dr. John B. Farley, 1612 Tremont Place, Denver 2.

Delaware: *Examination and Endorsement.* Dover, June 12-14 and July 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

District of Columbia:* *Examination.* Washington, June 13-14. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., N.W., Washington 6.

Florida:* *Examination.* Miami Beach, June 19-21. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

Georgia: *Examination and Reciprocity.* Atlanta, June. Sec., Mr. Cecil L. Clifton, 224 State Capitol, Atlanta 3.

Guam: *Subject to Call.* Act Sec., Dr. F. L. Conklin, Agana.

Idaho: *Examination and Endorsement.* Boise, July 11-13. Exec. Sec., Mr. Armand L. Bird, 304 Sonna Bldg., Boise.

Indiana: *Examination.* Indianapolis, June 22-24. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

Kentucky: *Examination.* Louisville, June 6-7. Sec., Dr. Russell E. Teague, 620 South Third St., Louisville 2.

Louisiana: *Examination and Reciprocity.* New Orleans, June 9-11. Sec., Dr. Edwin H. Lawson, 930 Hibernia Bank Bldg., New Orleans 12.

Maryland: *Examination.* Baltimore, June 15-18. Sec., Dr. Frank K. Morris, 1215 Cathedral St., Baltimore 1.

Michigan:* *Examination.* Ann Arbor and Detroit, June 6-8. Sec., Dr. E. C. Swanson, 118 Stevens T Mason Bldg., Lansing.

Mississippi: *Examination.* Jackson, June. Sec., Dr. A. L. Gray, Old Capitol, Jackson 13.

Montana: *Examination and Reciprocity.* Helena, April 5. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

Nebraska:* *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada:* *Examination and Reciprocity and Endorsement.* Reno, March 8. Sec., Dr. G. H. Ross, 112 No. Curry St., Carson City.

New Hampshire: *Examination.* Concord. March 9-12. Sec., Dr. Edward W. Colby, 61 South Spring St., Concord.

New Mexico:* *Examination and Reciprocity.* Santa Fe, May 16-17. Sec., Dr. R. C. Derbyshire, 227 East Palace Ave., Santa Fe.

New York: *Examination.* Albany, Buffalo, New York City, Rochester and Syracuse, June 28-July 1. Sec., Dr. Stiles D. Ezell, 23 S. Pearl Street, Albany.

North Carolina: *Endorsement.* Raleigh, May 9. *Examination and Endorsement.* Raleigh, June 20-23. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

North Dakota: *Examination and Reciprocity.* Grand Forks, July 6-9. Sec., Dr. C. J. Glaspel, Grafton.

Ohio: *Reciprocity.* Columbus, April 5 and June 17. *Examination.* Columbus, June 16-18. Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

Oklahoma:* *Examination and Endorsement.* Oklahoma City, May 31-June 1. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

Oregon:* *Reciprocity and Endorsement.* Portland, April 14-16. *Examination.* Portland, July. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

Pennsylvania: *Examination.* Philadelphia and Pittsburgh, July 5-7. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

Rhode Island:* *Endorsement.* Providence, March 24. *Examination.* Providence, April 7-8. Administrator of Professional Regulations, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

South Carolina: *Endorsement.* Myrtle Beach, May 17. *Examination.* Columbia, June 28-29. Sec., Dr. Harold E. Jervey, Jr., 1329 Blanding St., Columbia.

Tennessee:* *Examination.* Memphis, March 23-24. Sec., Dr. Alfred D. Mason, Jr., 1635 Exchange Bldg., Memphis 3.

Texas:* *Examination and Reciprocity.* Fort Worth, June 20-22. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

Utah: *Examination.* Salt Lake City, July 6-8. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

Virgin Islands: *Examination.* Charlotte Amalie, St. Thomas, June 8-9. Sec., Dr. Benjamin A. Nath, Charlotte Amalie, St. Thomas.

Virginia: *Examination and Reciprocity.* Richmond, June 13-17. Address: Board of Medical Examiners, 631 First St. S.W., Roanoke.

West Virginia: *Examination and Reciprocity.* Charleston, April 18. Sec., Dr. Newman H. Dyer, State Office Bldg. No. 3, Charleston 5.

Wyoming: *Examination and Reciprocity.* Cheyenne, June 6. Acting Sec., Dr. Carleton D. Anton, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Arizona: *Examination.* Tucson, March 18. *Endorsement.* Tucson, March 15. Sec., Mr. Herman E. Bateman, University of Arizona, Tucson.

Arkansas: *Examination.* Little Rock, April 21-22. Sec., Dr. A. W. Ford, Department of Education, Education Bldg., Little Rock.

District of Columbia: *Examination.* Washington, May 23-24. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., Washington 6.

Florida: *Examination.* Miami, June 4. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

Iowa: *Examination and Reciprocity.* Des Moines, April 12. Sec., Mr. Elmer W. Hertel, Wartburg College, Waverly.

Kansas: *Examination.* Kansas City, June 10-12. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

Minnesota: *Examination.* Minneapolis, April 5-6. Sec., Dr. Raymond N. Bieter, 165 Millard Hall, University of Minnesota, Minneapolis.

Nebraska: *Examination.* Omaha, May 3-4. Sec., Mr. R. K. Kirkman, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada: *Examination.* Reno, March. Sec., Dr. Kenneth C. Kemp, Box 9355, University of Nevada, Reno.

Oklahoma: *Examination.* Oklahoma City, April 15-16. Exec. Sec., Mrs. E. L. Haidek, 813 Braniff Bldg., Oklahoma City.

South Dakota: *Examination and Reciprocity.* Vermillion, June 10-11. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

Tennessee: *Examination.* Memphis and Nashville, March 23-24. Sec., Dr. O. W. Hyman, 62 S. Dunlap St., Memphis.

Texas: *Examination.* Austin, Houston and Galveston. Sec., Dr. Cornelia M. Smith, State Office Bldg., 201 East 14th St., Austin.

Washington: *Examination.* Seattle, July 13-14. Administrator, Mr. Thomas A. Carter, Department of Licenses, Capitol Bldg., Olympia.

Wisconsin: *Examination.* Madison, April 9. Milwaukee, June 4. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

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*Basic Science Certificate required.

DEATHS

Allen, Clarence Genon Ⓜ Commerce, Texas; Baylor University College of Medicine, Dallas, 1913; served on the medical staff of the East Texas State Teachers College; fellow of the American College of Surgeons; owner of the Allen Hospital; died Dec. 27, aged 68.

Allen, William Dean Hall Ⓜ Tallulah, La.; Tulane University School of Medicine, New Orleans, 1935; died in the Parker Hospital, Jackson, Dec. 11, of liver disease, aged 48.

Alvarez, Manuel, Bluffs, Ill.; Dearborn Medical College, Chicago, 1904; died in Jacksonville Dec. 21, aged 86.

Anderman, Sigurd Ⓜ New York City; Karl-Franzens-Universität Medizinische Fakultät, Graz, Austria, 1920; died of congestive heart failure, Dec. 17, aged 65.

Anderson, Jacob Campbell, Rockford, Tenn.; Tennessee Medical College, Knoxville, Tenn., 1891; died Dec. 23 of acute atypical pneumonia, aged 95.

Apfelberg, Isidor Ⓜ New York City; University and Bellevue Hospital Medical College, New York City, 1909; member of the American Academy of Dermatology and Syphilology; died of cerebral accident in the Columbus Hospital Oct. 22, aged 71.

Arnold, Hermann Bruno Ⓜ New Haven, Conn.; born in New Haven Oct. 27, 1902; Yale University School of Medicine, New Haven, 1926; in 1947 appointed to the State Board of Examiners for Physiotherapy Technicians; specialist certified by the American Board of Physical Medicine and Rehabilitation; certified by the National Board of Medical Examiners; member of the American Academy of Physical Medicine and Rehabilitation; veteran of World War II; served on the board of health of Woodbridge; associated with the New Haven area of the Rehabilitation Center, State of Connecticut Veterans Home and Hospital in Rocky Hill, and the Hospital of St. Raphael; died Jan. 7, aged 57.

Bailey, Archie Charles Ⓜ Nashville, Tenn.; University of Nashville Medical Department, 1899; formerly on the faculty of his alma mater; died Dec. 14, aged 92.

Baze, Perry Allen Ⓜ Mason, Texas; Memphis (Tenn.) Hospital Medical College, 1902; veteran of World War I; associated with the Mason Memorial Hospital; died of arteriosclerotic heart disease Dec. 6, aged 82.

Beck, Frank William Ⓜ Erie, Pa.; College of Physicians and Surgeons, Baltimore, 1903; died in St. Vincent Hospital Dec. 14, aged 86.

Billingsley, Paul Raymond Ⓜ Sioux Falls, S. D.; Northwestern University Medical School, Chicago, 1918; fellow of the American College of Surgeons; past-president of the staff of the McKennan Hospital, where he died of coronary occlusion Dec. 11, aged 72.

Blanton, Wyndham Bolling Ⓜ Richmond, Va.; born in Richmond June 3, 1890; Columbia University College of Physicians and Surgeons, New York City, 1916; specialist certified by the American Board of Internal Medicine; in 1937 member of the House of Delegates of the American Medical Association; past-president of the Richmond Society of Internal Medicine and Richmond Academy of Medicine; formerly vice-president of the American Academy of Allergy and the Southern Medical Association, member of the American Clinical and Climatological Association, Virginia Academy of Science, Industrial Medical Association, American Association of the History of Medicine, Pi Kappa Alpha, Phi Chi, Omicron Delta Kappa, Sigma Delta Chi, and the Phi Beta Kappa; fellow of the American College of Physicians; professor emeritus of clinical medicine and the history of medicine at the Medical College of Virginia, where he was named associate professor of medicine in 1930, professor of the history of medicine in 1933, and professor of clinical medicine in 1939; veteran of World War I; senior surgeon in the U. S. Public Health Service Reserve; associated with the Richmond Memorial Hospital; in 1933 received the honorary degree of doctor of literature from Hampden-Sidney College, in recognition of his work on the "History of Medicine in Virginia"; editor emeritus of the *Virginia Medical Monthly;* consulting editor of the *Journal of the History of Medicine and Allied Sciences* and the *Bulletin of the History of Medicine;* past-associate editor of the *Annals of Medical History;* chairman of the board of trustees of Union Theological Seminary; died Jan. 6, aged 69.

Bossak, Solomon Ⓜ New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1907; served on the staffs of the Bronx, Mount Sinai, Lincoln, and Harlem hospitals; died of a heart attack in the Fort Pierce (Fla.) Memorial Hospital Dec. 23, aged 75.

Ⓜ Indicates Member of the American Medical Association.

Bremer, John Lewis Ⓜ Cohasset, Mass.; Harvard Medical School, Boston, 1901; served on the faculty of his alma mater; veteran of World War I; died in Boston Dec. 25, aged 85.

Briggs, Stewart Daniel, Shelton, Wash.; State University of Iowa College of Medicine, Iowa City, 1904; died in the Shelton General Hospital Dec. 18, aged 94.

Brown, Asa Willis, Bluffton, Ind.; Indiana Medical College, School of Medicine of Purdue University, Indianapolis, 1906; served as county coroner and city health officer; died of carcinoma of the prostate Dec. 8, aged 82.

Bryant, Clara Davis Ⓜ Lansdowne, Pa.; Woman's Medical College of Pennsylvania, Philadelphia, 1926; member of the American Academy of General Practice; certified by the National Board of Medical Examiners; past-president of the Delaware County Medical Society; served on the faculty of her alma mater; associated with the Thomas M. Fitzgerald Mercy Hospital in Darby, Delaware County Hospital in Drexel Hill, Hospital of the Woman's Medical College of Pennsylvania, Philadelphia, and the Hospital of the University of Pennsylvania in Philadelphia; died Dec. 23, aged 57.

Burdeshaw, Shelby L. Ⓜ Headland, Ala.; University of Nashville (Tenn.) Medical Department, 1908; died Dec. 13, aged 79.

Carr, Curtis Grube, Los Angeles; Howard University College of Medicine, Washington, D. C., 1925; died Dec. 25, aged 60.

Carter, James Johnston Ⓜ Biloxi, Miss.; Tulane University School of Medicine, New Orleans, 1921; on the staff of the Biloxi Hospital; died in the Southern Baptist Hospital, New Orleans, Jan. 1, aged 68.

Cary, Remus Griffith, Sorgho, Ky.; Kentucky School of Medicine, Louisville, 1897; died Dec. 27, aged 88.

Challenger, Chester John Ⓜ Chicago; Dearborn Medical College, Chicago, 1906; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; veteran of World War I; associated with the St. Mary of Nazareth Hospital, where he was past-president of staff; died in St. Francis Hospital, Evanston, Dec. 29, aged 76.

Chapman, Bertrand A. Ⓜ Springfield, Vt.; Baltimore Medical College, 1895; on the staff of the Springfield Hospital; died Dec. 9, aged 91.

Cheek, Pratt Jr., Raleigh, N. C.; Emory University School of Medicine, Atlanta, 1940; interned at the Georgia Baptist Hospital in Atlanta, where he served a residency at the Grady Hospital; veteran of World War II; died of heart failure Dec. 7, aged 45.

Clark, Lloyd Houghton, Penfield, N. Y.; New York Homeopathic Medical College and Flower Hospital, New York City, 1908; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; served on the staffs of the Genesee and Park Avenue hospitals in Rochester, N. Y.; died of paralysis agitans Dec. 24, aged 75.

Clark, Tracy H., Chicago; Northwestern University Medical School, Chicago, 1898; died of arteriosclerotic heart disease Dec. 29, aged 87.

Cleveland, Robert Henry Ⓜ Jacksonville, Fla.; Medical College of Georgia, Augusta, 1939; interned at the Duval County Hospital in Jacksonville and served a residency at the St. Louis Children's Hospital in St. Louis; affiliated with Baptist Memorial Hospital, St. Vincent's Hospital, St. Luke's Hospital, and the Duval Medical Center; died of acute coronary occlusion Dec. 28, aged 47.

Cliff, William Mundell Ⓜ Chatham, N. J.; Queen's University Faculty of Medicine, Kingston, Ont., Canada, 1931; veteran of World War II; for many years on the staff of the Veterans Administration in Newark; died of acute coronary occlusion Dec. 28, aged 52.

Cody, Claude Carr Jr. Ⓜ Houston, Texas; born in Georgetown Sept. 9, 1884; Johns Hopkins University School of Medicine, Baltimore, 1910; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Laryngological Association, and the American Laryngological Rhinological and Otological Society; fellow of the American College of Surgeons; chairman, Section on Laryngology, Otology and Rhinology of the American Medical Association, 1942-1943; past-president of the State Medical Association of Texas, Harris County Medical Society, and the Texas Ophthalmological and Otolaryngological Society; veteran of World War I; the Cody Memorial Library at Southwestern University, Georgetown, where he was a member of board of trustees, was named in his honor; associated with the Houston Eye, Ear, Nose and Throat Hospital; died of apoplectic stroke in the Methodist Hospital Dec. 30, aged 75.

Coletti, John Milton Ⓜ Salt Lake City, Utah; University of Nebraska College of Medicine, Omaha, 1934; specialist certified by the American Board of

Dermatology; member of the American Academy of Dermatology and Syphilology; clinical assistant in dermatology at the University of Utah College of Medicine; member and past-president of the staff of the Holy Cross Hospital; died of infarction of the myocardium Dec. 25, aged 50.

Cooper, David Gordon Ⓜ Albion, N. Y.; University of Buffalo School of Medicine, 1909; veteran of World War I; for many years chief of staff at the Arnold Gregory Memorial Hospital, where he died Dec. 30, aged 73.

Cottongim, Jay Gould Ⓜ Jackson, Tenn.; University of Tennessee College of Medicine, Memphis, 1914; veteran of World War I; died of acute myocardial infarction Dec. 21, aged 67.

Croacher, Anna Wood, New Bedford, Mass.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1891; died Dec. 15, aged 91.

Crossen, Robert James Ⓜ Chapel Hill, N. C.; Washington University School of Medicine, St. Louis, 1925; specialist certified by the American Board of Obstetrics and Gynecology; member of the Central Association of Obstetricians and Gynecologists and the American Radium Society; fellow of the American College of Surgeons; certified by the National Board of Medical Examiners; served as associate clinical professor of obstetrics and gynecology at his alma mater; formerly associated with Barnes, St. Louis Maternity, St. Louis Children's, and St. Luke's hospitals; died Dec. 19, aged 61.

Curtin, Joseph Justin Ⓜ Greendale, Wis.; Milwaukee Medical College, 1910; served on the staff of the Misericordia Hospital in Milwaukee; died in St. Francis Hospital, Milwaukee, Dec. 15, aged 73.

Daniels, Philip Brock Ⓜ Keene, N. H.; University of Vermont College of Medicine, Burlington, 1930; past-president of the Cheshire County Medical Society; veteran of World War II and was awarded the Bronze Star and the Purple Heart; certified by the National Board of Medical Examiners; associated with the Elliot Community Hospital, where he was past-president of the medical staff, and where he died of chronic pyelonephritis Dec. 27, aged 55.

Dean, Joseph Charles Ⓜ Madison, Wis.; University of Pennsylvania School of Medicine, Philadelphia, 1930; member of the founders group of the American Board of Surgery; fellow of the American College of Surgeons; served as vice-president of the state board of health; veteran of World War II; on the staff of St. Mary's Hospital; died Dec. 24, aged 53.

Deitrick, George Albert Ⓜ Sunbury, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1910; fellow of the American College of Surgeons; served as state senator; associated with the Mary M. Packer Hospital; served overseas during World War I; died in the Sunbury Community Hospital Dec. 10, aged 72.

Doering, Frank L. Ⓜ Pittsburgh; Hahnemann Medical College and Hospital, Philadelphia, 1924; veteran of World War I; member of the staff of the Shadyside Hospital; died Dec. 18, aged 61.

Dupont, Hanson Louis Ⓜ Houma, La.; Tulane University School of Medicine, New Orleans, 1944; interned at the Shreveport Charity Hospital in Shreveport, La.; served a residency at the Charity Hospital of Louisiana in New Orleans; served in the U. S. Naval Reserve from Aug. 6, 1945, to Aug. 13, 1946; died of skull fracture Dec. 11, aged 38.

Eiseman, Paul Claire Ⓜ Latrobe, Pa.; Jefferson Medical College of Philadelphia, 1917; fellow of the American College of Surgeons; veteran of World War I; served on the staff of the Latrobe Hospital, where he died of coronary occlusion Jan. 6, aged 65.

Fitzpatrick, Charles Monroe, Lesterville, Mo.; American Medical College, St. Louis, 1907; died in the Missouri Baptist Hospital, St. Louis, Dec. 12, of heart disease, aged 80.

Foster, Edwin L. Ⓜ Arvada, Colo.; Hospital College of Medicine, Louisville, Ky., 1890; served as president of the Arvada School Board; died Jan. 2, of old age, aged 94.

Franklin, Charles Edward Ⓜ Oak Park, Ill.; University of Cincinnati College of Medicine, 1930; member of the Radiological Society of North America; past-president of the Aux Plaines Branch of the Chicago Medical Society; past-president of the staff of the Oak Park Hospital; veteran of World War II; died of heart failure Jan. 6, aged 55.

Frisbie, Gertrude Flint, Lowell, Mass.; Tufts College Medical School, Boston, 1928; served on the staff of St. Joseph's Hospital, where she died Dec. 23, aged 72.

Garber, Max D. Ⓜ Mansfield, Ohio; Indiana University School of Medicine, Indianapolis, 1934; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; served as health officer of Kosciusko County, Ind.; president of the Mansfield Board of Education; served on the staff of the Strong Memorial–Rochester Municipal Hospital, Rochester, N. Y.; died of coronary thrombosis Jan. 2, aged 49.

Gasser, William Pope Ⓜ Loveland, Colo.; University of Colorado School of Medicine, Denver, 1920; served as vice-president of the state board of health; veteran of World War I; died in the Veterans Administration Hospital, Denver, of multiple cerebral vascular accident Dec. 11, aged 55.

Gatewood, Emmett Trible Ⓜ Richmond, Va.; born in 1886; Medical College of Virginia, Richmond, 1910; since 1958 professor emeritus at his alma mater, where he joined the faculty as an instructor of otolaryngology in 1920 and became clinical professor in 1944; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Laryngological, Rhinological and Otological Society, and the American Broncho-Esophagological Association; fellow of the American College of Surgeons; past-president of the Richmond Ophthalmological and Otolaryngological Society, Richmond Academy of Medicine, and the Virginia Society of Ophthalmology and Otolaryngology; associated with the Johnston–Willis Hospital and the Medical College of Virginia Hospital; died of coronary occlusion Jan. 5, aged 73.

Gattens, Wilber Elton, Frostburg, Md.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1925; died in the Miners Hospital Dec. 14, aged 59.

Gay, Fritz Walter Ⓜ Newport, N. H.; Harvard Medical School, Boston, 1902; veteran of World War I; fellow of the American College of Surgeons; past-president of the Middlesex South District Medical Society, Mass.; formerly practiced in Malden, Mass., where he was associated with the Malden Hospital, for many years a director of the First National Bank, member of the school committee, and a trustee of the Malden Public Library; died Dec. 25, aged 84.

Geiger, Carl Joseph Ⓜ Syracuse, N. Y.; Syracuse University College of Medicine, 1910; served on the faculty of his alma mater; school physician; past-president of the Syracuse Academy of Medicine and the Onondaga County Medical Society; veteran of World War II; at one time assistant superintendent of the Rhode Island Hospital in Providence; associated with the Syracuse Memorial Hospital; died Dec. 28, aged 72.

Gerdes, Maude Marguerite Ⓜ Miles City, Mont.; University of Minnesota Medical School, Minneapolis, 1930; member of the Central Association of Obstetricians and Gynecologists; certified by the National Board of Medical Examiners; formerly on the faculty of her alma mater; served as consultant in obstetrics for the Children's Bureau, Washington, D. C., and director of maternal and child health of the Mississippi State Board of Health at Jackson; at one time health officer of Big Horn County Health Department; died of heart failure in Montevideo, Minn., Dec. 27, aged 57.

Ginley, Francis Michael Ⓜ Dunmore, Pa.; Jefferson Medical College of Philadelphia, 1916; member of the American Psychiatric Association; past-president of the Lackawanna County Medical Society; veteran of World War I; member of the draft board during World War II; served on the staffs of the Farview State Hospital in Waymart, Mercy Hospital, Scranton State Hospital, St. Mary's Hospital, and the Moses Taylor Hospital in Scranton, where he died Dec. 9, aged 66.

Goeth, Richard Anton Ⓜ San Antonio, Texas; University of Texas School of Medicine, Galveston, 1894; died Jan. 1, aged 85.

Grieumard, George Auguste, Fitchburg, Mass.; Baltimore University School of Medicine, 1894; veteran of World War I; died in Gardner Dec. 22, aged 92.

Haenszel, Allen Lee Ⓜ San Bernardino, Calif.; University of Buffalo School of Medicine, 1908; member of the American Academy of Medicine; for many years physician for the Santa Fe Railroad; died Dec. 13, aged 74.

Hamilton, Birch Jacob, Detroit; Chicago College of Medicine and Surgery, 1915; veteran of World War I; died Dec. 21, aged 71.

Hamilton, David Doom Ⓜ Springfield, Colo.; University of Texas School of Medicine, Galveston, 1896; died of uremia Dec. 8, aged 84.

Hand, Fordus Victor Ⓜ Detroit; University of Michigan Medical School, Ann Arbor, 1933; veteran of World War II; associated with Evangelical Deaconess Hospital; died Dec. 23, aged 53.

Hausman, Samuel William Ⓜ Wyckoff, N. J.; Syracuse University College of Medicine, 1916; past-president of the Monmouth County Medical Society; for many years served on the Red Bank Board of Health and formerly on the staff of the Riverview Hospital; died in Bradenton, Fla., Jan. 1, aged 73.

Hermann, Edward, Newport, Ky.; Miami Medical College, Cincinnati, 1903; served as president of the board of education; formerly associated with the William Booth Memorial Hospital and St. Elizabeth Hospital in Covington, and the Speers Memorial Hospital in Dayton; died in St. Luke Hospital of Campbell County, Fort Thomas, Dec. 10, aged 80.

Herzfeld, Melvin Gustav, St. Louis; Columbia University College of Physicians and Surgeons, New York City, 1911; veteran of World Wars I and II; formerly associated with the regional office of the Veterans Administration; died of arteriosclerotic heart disease Dec. 29, aged 73.

Hethcock, John C., Los Angeles; National University of Arts and Sciences Medical Department, St. Louis, 1915; died of a heart attack in the Good Samaritan Hospital Dec. 18, aged 71.

Higgins, Raymond Dyer Ⓜ San Francisco; University of Vermont College of Medicine, Burlington, 1918; interned at the Maine General Hospital in Portland, Me., where he served a residency; associated with the U. S. Public Health Service; chief deputy medical officer in charge of the U. S. Public Health Service Hospital; served on the staff of the U. S. Public Health Service Hospital in Staten Island; died Dec. 20, aged 40.

Himmelstein, Aaron Ⓜ New York City; born in New York City Jan. 5, 1914; Cornell University Medical College, New York City, 1937; interned at the Morrisania City Hospital in New York City; served a residency at the Bellevue Hospital in New York City; specialist certified by the American Board of Surgery and founder member of the Board of Thoracic Surgery; member of the Society of University Surgeons, American Association for Thoracic Surgery, and the American Trudeau Society; veteran of World War II; fellow of the American College of Surgeons; on the faculty of Columbia University College of Physicians and Surgeons; consultant at the U. S. Naval Hospital in St. Albans, N. Y., and the Veterans Administration Hospital in Manhattan; served on the staffs of the Mount Sinai Hospital, Presbyterian Hospital and the Bellevue Hospital Center; died of respiratory failure in the Neurological Institute of Columbia–Presbyterian Hospital Dec. 18, aged 45.

Howland, Clifford, Enfield, N. H.; Dartmouth Medical School, Hanover, 1908; died in the Mary Hitchcock Memorial Hospital, Hanover, Dec. 24, aged 81.

Jones, John Gulick Ⓜ Cresson, Pa.; Jefferson Medical College of Philadelphia, 1948; interned at U. S. Marine Hospital in Baltimore; served a residency at the Delaware County Hospital in Drexel Hill; member of the American Trudeau Society; veteran of World War II; associated with the Laurence F. Flick State Hospital, where he died Dec. 24, aged 36.

Kampschmidt, William Frederick, St. Paul; University of North Carolina School of Medicine, Chapel Hill, N. C., 1955; interned at the City Memorial Hospital in Winston–Salem, where he served a residency; served a residency at the Charles T. Miller Hospital, where he died Dec. 13, aged 32.

Kantor, Dominic Benjamin, Fairbury, Neb.; University of Nebraska College of Medicine, Omaha, 1923; veteran of World War I; died Dec. 28, aged 67.

Kennard, William Sorrento, Newark, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1911; died Jan. 1, aged 81.

Kneucker, Alfred Walter, Chicago; born in Vienna, Austria, June 30, 1904; Medizinische Fakultät der Universität, Vienna, 1929; assistant professor of surgery at Chicago Medical School; at various times chief of the department of urology, General Hospital of Shanghai, China, head of the department of physiology, Riverside (Calif.) College, and visiting professor of the University of California, Santa Barbara; fellow of the International College of Surgeons; discovered that the kidney gives an electric potential; published two books and many papers; on the staffs of the American, Northwest and Mount Sinai hospitals; was lecturing in Europe on his research on the problem of human deaths when he died of coronary occlusion in Vienna, Jan. 12, aged 55.

Kraemer, Samuel Harry Ⓜ Jersey City, N. J.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1930; died of coronary occlusion Nov. 21, aged 54.

Krolicki, Thaddeus Alphonsus Ⓜ Providence, R. I.; born in Bridgeport, Conn., Dec. 19, 1904; St. Louis University School of Medicine, 1929; specialist certified by the American Board of Proctology; member of the American Proctologic Society and the American College of Gastroenterology; fellow of the American College of Surgeons and the International College of Surgeons; past-president of the Pawtucket Medical Association; for a time school physician in Pawtucket; for many years state medical examiner; served on the staffs of the Memorial Hospital in Pawtucket, State Hospital for Mental Diseases, Howard, Roger Williams General and St. Joseph's hospitals in Providence, Our Lady of Fatima Hospital in North Providence, and the Notre Dame Hospital in Central Falls; died Dec. 12, aged 54.

McGannon, Francis Lambert Ⓜ Lakewood, Ohio; Western Reserve University College of Medicine, Cleveland, 1929; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Laryngological, Rhinological and Otological Society, American Society of Ophthalmologic and Otolaryngologic Allergy, of which he was past-president, and the American College of Allergists; fellow of the American College of Surgeons; associated with St. John's Hospital, where he died Dec. 26, aged 56.

Martone, Edward Jay Ⓜ Brooklyn; George Washington University School of Medicine, Washington, D. C., 1931; died in the Wyckoff Heights Hospital Dec. 5, aged 54.

Nace, Alvia George Ⓜ Tacoma, Wash.; University Medical College of Kansas City, Mo., 1909; veteran of World War I; an active and honorary member of St. Josephs, Tacoma General, and Mountain View General hospitals; died Nov. 24, aged 77.

Schwartz, Frederick Ⓜ Brooklyn; University and Bellevue Hospital Medical College, New York City, 1930; certified by the National Board of Medical Examiners; specialist certified by the American Board of Surgery; clinical instructor in surgery at the State University of New York, Downstate Medical Center and the New York Medical College; fellow of the International College of Surgeons; veteran of World War II; on the staffs of the Morrisania City Hospital in New York City, the Jewish Chronic Disease Hospital and the Maimonides Hospital; died Dec. 26, aged 53.

Shelton, Josephine Annette Ⓜ Refugio, Texas; Baylor University College of Medicine, Dallas, 1938; interned at the Hospital for Women in Baltimore; died Dec. 25, aged 47.

Stewart, Helen Montgomery, Chambersburg, Pa.; Woman's Medical College of Pennsylvania, Philadelphia, 1911; died Dec. 5, aged 75.

Stewart, Milton B. Ⓜ Logansport, Ind.; Cleveland Medical College, Homeopathic, 1897; for many years county coroner; died in the Memorial Hospital Dec. 17, aged 86.

Strobach, Rolla Lenox, Kansas City, Kan.; Washington University School of Medicine, St. Louis, 1936; interned at St. John's Hospital in St. Louis; service with the U. S. Public Health Service terminated Aug. 4, 1946; associated with the Providence Hospital, St. Margaret's Hospital, and the Bethany Hospital, where he died Dec. 23, aged 49.

Sutherland, Wade Hampton Ⓜ Booneville, Miss.; Memphis (Tenn.) Hospital Medical College, 1904; member of the Southeastern Surgical Congress and the American College of Chest Physicians; fellow of the International College of Surgeons and the American College of Surgeons; on the staff of the Northeast Mississippi Hospital; died Dec. 16, aged 83.

Switzer, John Wesley Ⓜ North Palm Beach, Fla.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1921; fellow of the American College of Surgeons; formerly associated with the Hamot Hospital in Erie, Pa.; died in the St. Mary's Hospital, West Palm Beach, Dec. 22, aged 67.

Tannenbaum, Karl Hart Ⓜ Frederick, Md.; Johns Hopkins University School of Medicine, Baltimore, 1918; formerly practiced in Chicago, where he taught at Northwestern University Medical School and was on the staff of St. Luke's Hospital; died in the Chicago Wesley Memorial Hospital Dec. 23, aged 67.

Taylor, Duane Russell Ⓜ Portland, Ore.; Washington University School of Medicine, St. Louis, 1948; interned at St. Louis City Hospital; served a residency at the Veterans Administration Hospital in Jefferson Barracks, Mo.; veteran of World War II; formerly associated with the Veterans Administration; affiliated with the Physicians and Surgeons Hospital, Emanuel Hospital, and the Good Samaritan Hospital, where he died Dec. 6, aged 38.

Thomas, Victor F., Evans City, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1889; died in the Butler County Memorial Hospital in Butler Dec. 5, aged 96.

Tinsley, Helen M. Frost, Palo Alto, Calif.; Stanford University School of Medicine, San Francisco, 1950; interned at San Francisco Hospital; from 1954 to 1956 a member of the Atomic Bomb Casualty Commission in Japan; died in the Palo Alto–Stanford Hospital Dec. 6, aged 35.

Toth, John Joseph Ⓜ Chebanse, Ill.; Chicago Medical School, 1944; interned at St. Joseph Hospital in Elgin; veteran of World War II; member of the American Academy of General Practice; associated with St. Mary's Hospital in Kankakee; died Dec. 7, aged 50.

Towle, Murray Hanson Ⓜ Manchester, N. H.; Dartmouth Medical School, Hanover, 1909; veteran of World War I; chairman of the Manchester Board of Health; on the staff of the Sacred Heart Hospital; died Dec. 21, aged 75.

Treichler, Albert Julius Ⓜ Lieut. Col., U. S. Army, retired, Kentfield, Calif.; Universita degli Studi di Roma, Facolta di Medicina e Chirurgia, Italy, 1902; veteran of World Wars I and II; retired from the U. S. Army Feb. 29, 1940; died in the Letterman Army Hospital, San Francisco, Dec. 18, aged 83.

Vandenberg, Bernice Helen, Pittsburgh; University of Wisconsin Medical School, Madison, 1956; interned at the Presbyterian Hospital of Pittsburgh; served a residency at the Western Psychiatric Institute; died Nov. 28, aged 30.

Vincent, Charles P. Ⓜ Laurens, S. C.; Baltimore Medical College, 1907; on the staff of the Laurens County Hospital; died Dec. 5, aged 76.

Vose, Robert Henry Ⓜ Milton, Mass.; Harvard Medical School, Boston, 1896; veteran of World War I; died Dec. 18, aged 89.

Wallace, Benjamin Cicero Jr. Ⓜ Waxahachie, Texas; Tulane University School of Medicine, New Orleans, 1935; past-president and secretary of the Ellis County Medical Society; fellow of the American College of Physicians; served as vice-president of the Texas Heart Association and the Scott and White Alumni Association; veteran of World War II; associated with the Waxahachie Sanitarium; died in Dallas Dec. 7, aged 50.

Wallin, William B. Ⓜ Brooksville, Ky.; University of Louisville (Ky.) Medical Department, 1893; served on the Bracken County Board of Education; in 1954 named Kentucky Doctor of the Year by the Kentucky State Medical Association; a director of the First National Bank; past-president of the Bracken County Medical Society; served on the staff of the Hayswood Hospital in Maysville; died Dec. 16, aged 89.

Wead, John Trimmer Ⓜ Wyoming, Ill.; University of Illinois College of Medicine, Chicago, 1924; veteran of World War I; associated with the Methodist Hospital, Peoria, where he died Dec. 22, aged 63.

Weinberg, Joseph, Jackson Heights, N. Y.; Cornell University Medical College, New York City, 1900; retired chief medical examiner for the department of sanitation; died in the Bayside (N. Y.) Gardens Nursing Home Dec. 28, aged 80.

Wendel, Elmer John Ⓜ Rochester, N. Y.; University of Buffalo School of Medicine, 1907; veteran of World War I; served on the board of directors of the Park Avenue Hospital, where he was a member of the staff; died Dec. 25, aged 76.

Wilder, Russell Morse Ⓜ Rochester, Minn.; born in Cincinnati Nov. 24, 1885; Rush Medical College, Chicago, 1912; on Oct. 1, 1919, entered the Mayo Clinic as an associate in the division of medicine and assistant professor of medicine in the Mayo Foundation; in 1929 left the clinic to become professor of medicine and chairman of the department of medicine in the University of Chicago; on Oct. 1, 1931, returned to the Mayo Clinic and became professor of medicine in the Mayo Foundation and head of the department of medicine; retired from the Mayo Clinic and Mayo Foundation on Dec. 31, 1950; director of the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service in Bethesda, Md., from 1951 to 1953; honorary member, past-president, and vice-president of the American Diabetes Association, which in 1947 conferred the Banting Medal on him; the University of Chicago gave him the Distinguished Service Medal in 1941 and the Howard Taylor Ricketts Award in 1949; the Medical Alumni Association of the University of Chicago presented him with the honorary gold key in 1955; the American Medical Association honored him with the Joseph Goldberger award in 1954 and in 1956 the American Bakers' Association gave him an award in recognition of activities in promoting enrichment with vitamins of white flour and bread; elected president of the National Vitamin Foundation in 1956; chairman, Section on Pharmacology and Therapeutics of the American Medical Association, 1930-1931 and served on its Council on Foods and Nutrition, 1931-1951; specialist certified by the American Board of Internal Medicine; member of the Association of American Physicians, Central Society for Clinical Research, American Society for Clinical Investigation, and the American Society for Experimental Pathology; fellow of the American College of Physicians; held membership in the Society of the Sigma Xi, Alpha Omega Alpha, Nu Sigma Nu, and Delta Kappa Epsilon; member of the committee on medicine of the National Research Council from 1940 to 1946, and chairman of that committee in 1940; in 1941 organized and became the chairman of the Food and Nutrition Board, serving on that board from 1941 to 1947; in 1943 was chief of the Civilian Food Requirements Branch of the War Food Administration, Washington, D. C.; veteran of World War I; from 1941 to 1946 was a member of the editorial board of the *Journal of Nutrition;* from 1932 to 1950 served on the editorial board of the *Archives of Internal Medicine;* in 1942 became a member of the editorial committee of *Nutrition Reviews* and in 1952 appointed an associate editor of *Public Health Reports;* author of "Primer for Diabetic Patients" and "Clinical Diabetes Mellitus and Hyperinsulinism; contributor to several textbooks on medicine and to the Encyclopædia Britannica; died in St. Mary's Hospital Dec. 16, aged 74.

Wilkins, George Clarence Ⓜ Manchester, N. H.; Harvard Medical School, Boston, 1899; member of the founders group of the American Board of Surgery; past-president of the Manchester Medical Association, Hillsborough County Medical Society, and New Hampshire Medical Society; member of the American Radium Society; fellow of the American College of Surgeons; veteran of World War I; served as chairman of the state cancer commission; for many years member and president of the state board of health; consultant, Veterans Administration Hospital; associated with the Elliot Hospital, where he was past-president of the medical staff, and where he died Dec. 6, aged 83.

Williams, William George, Brownwood, Texas; Memphis (Tenn.) Hospital Medical College, 1902; veteran of World War I and the Spanish-American War; died in the Medical Arts Hospital Dec. 6, aged 85.

Williamson, Ora Monroe, Sedona, Ariz.; Barnes Medical College, St. Louis, 1907; veteran of World War I; died in the Whipple (Ariz.) Veterans Administration Center Dec. 17, aged 78.

Wilson, John G. Ⓜ Keo, Ark.; Kansas City (Mo.) College of Medicine and Surgery, 1918; mayor of Keo; died in the Arkansas Baptist Hospital, Little Rock, Dec. 8, aged 92.

Wofford, William Earl, Cartersville, Ga.; Atlanta College of Physicians and Surgeons, 1913; past-president of the Bartow County Medical Society; veteran of World War I; died Dec. 14, aged 70.

Worden, John Edward, San Francisco; Northwestern University Medical School, Chicago, 1899; formerly associated with the Indian Service; served as health officer of Nevada and secretary of the state medical association; died Dec. 28, aged 84.

FOREIGN LETTERS

BRAZIL

Blood Transfusion Precaution.—Dr. R. I. Carvalho and co-workers (*Sangre* 4:26, 1959) recommended adding gentian violet to blood to be transfused. This precaution may prevent the spread of Brazilian trypanosomiasis, especially in highly endemic regions. Since there was some doubt about whether the erythrocytes which were treated with a concentration of gentian violet (1:4,000) sufficient to kill Trypanosoma cruzei would survive, the authors studied survival of red blood cells exposed to this concentration of the drug for 24 hours at 4 C, using radioactive chromium as a tracer. The mean cell life varied between 66 and 91 days. From this it was concluded that other properties of the red blood cells were not significantly changed, and the prophylactic use of gentian violet was considered practicable.

Cesarean Section.—Dr. B. Neme of the University of São Paulo stated that the obstetric future of patients subjected to cesarean section depends mainly on the uterine scar, the vitality of which depends on the type of the incision and the suture of the myometrium (*Rev. gynec. e obst.*, Nov., 1959). There is, however, no agreement as to the best kind of myometrial suture. The following elements are believed to be essential for a proper suture: perfect apposition of the edges of the uterine wound, preservation of local circulation, noninclusion of the endometrium, and nondiminution in the elasticity of the tissues.

Prophylactic Appendectomy.—Salvatore and Martins (*Rev. gynec. e obst.*, Nov., 1959) removed the appendix as a prophylactic measure in 250 gynecological laparotomies. In 58% of these there were histopathological changes typical of chronic appendicitis. They believed that this justified their procedure.

FRANCE

Blood Transfusions.—A. Suchet (Golden Book of the 1959 Congress of the Federation of Blood Donors) stated that the serologic test for syphilis and determination of the blood groups, which are usually the only examinations made, are not sufficient to protect the donor and the recipient in transfusions. Certain laboratory examinations may reveal chronic diseases in apparently healthy subjects and thus protect the recipient and the donor. Since a sedimentation rate is more significant than the number of leukocytes in the detection of latent infections, no blood should be transfused from a donor with an increased sedimentation rate, and because most such donors are unaware of their low sedimentation rate the results of a test may give them a timely warning. Alpha hemolytic streptococcus infections, such as rheumatic fever, may also be recognized in prospective donors with the aid of antistreptococcin. A test for mucoproteins which showed positive results in patients with chronic rheumatic fever or collagen diseases, which are frequently not recognized, or diseases of the reticuloendothelial system constitutes a further basis for rejecting a prospective donor and advising him to seek treatment.

The test for lipoproteins gives an accurate indication of the donor's vascular age. If an unrecognized abnormality is discovered the donor should not be bled frequently and in some cases should be rejected. This test was made in 1,000 subjects, and the findings were pathological in 21% of those aged 35 years or over, in 28% of those aged 45 years or over, in 30% of those aged 55 years or over, and in 47% of those aged 65 years or over. With the aid of a technique elaborated by the author all these indispensable examinations can be made rapidly and without great expense.

Determination of Circulatory Velocity.—J. Pieri and co-workers (*Presse méd.*, July 25, 1959) described a new technique for the direct determination of circulatory velocity. A histamine wheal is produced on the root of the thigh, the interior surface of the knee, the middle and external portion of the leg, the anterior surface of the ankle, and the root of the great toe. A needle is placed in the internal saphenous vein at the level of the malleolus. Then 10 ml. of a 5% solution of fluorescein is injected into the femoral artery at the site of the crural arch. The leg is examined in a dark room with the aid of a Wood light by estimating both the rapidity with which lighting up of the histamine wheals occurs and fluorescence appears in the venous blood. In order to obtain precise results the administration of all vasodilator drugs should be stopped at least 24 hours before the test, the systemic circulatory velocity should be determined previously, and the patient should be examined at a room temperature of 20 to 22 C.

The items in these letters are contributed by regular correspondents in the various foreign countries.

In a healthy person the appearance of fluorescence in the venous blood and the lighting up of the last wheal in the region of the great toe occurs at the same time (in less than 22 seconds). A delay in either or both indicates lesions caused by diffuse and massive overloading of the arterial tree. When the results of the classic fluoroscopy are normal and the appearance of fluorescence and the lighting up of the last wheal in the arteriovenous test do not occur within 22 seconds, the patient probably has arteritis or some deep-seated disorder of the capillary system.

Explosion of Flatus.—J. Guillotte (*Phlébologie*, no. 2, 1959) described an accident which occurred during a minor operation in which electrocoagulation was used in a 33-year-old man with hemorrhoids. The injection of a sclerosing substance into the hemorrhoidal swelling produced a significant hemorrhage. In order to stop the bleeding a glass anuscope was inserted and forceps were placed on the bleeding artery. Then an electrode was applied for coagulation. At that moment the patient passed flatus which caught fire and exploded. The patient became unconscious. Operation showed a 10-cm. (3.9-in.) laceration of the lower part of the sigmoid which was sutured. The patient sued the surgeon for malpractice, but the court ruled that the surgeon could not be blamed.

Withdrawal Therapy in Drug Addiction.—J. P. Temple and co-workers (*Thérapie*, no. 2, 1959) used dextromoramide (Pyrrolamidol or Palfium) to ameliorate withdrawal symptoms in drug addicts. Since prolonged treatment with this drug may cause a persistant psychic dependence on it, a rigidly controlled institutional environment and, in some patients, psychotherapy is required. The authors gave 650 to 700 mg. of cortisone daily. The administration of dextromoramide was discontinued after cortisone therapy had been given for 48 hours. The treatment with cortisone was continued in gradually decreasing doses for five or six more days, and then ACTH was given for a few days. This treatment brought about disappearance of the abstinence syndrome, sleep returned to normal, and a condition of euphoria ensued. The authors suggested that the drug addict should be given dextromoramide as a substitute for an equivalent dose of morphine derivatives for the period of at least one month, after which he should be given cortisone therapy.

Pentobarbital for Delirium Tremens.—J. Fours (*Anesthésie, Analgésie, Réanimation*, no. 4, 1958) gave pentobarbital intramuscularly to a series of 50 patients with delirium tremens. Given thus the drug was better tolerated than when given intravenously. With doses ranging from 2 to 2.5 Gm. every 8 hours for 24 hours a deep sleep was produced. It was necessary to watch the patient for at least 45 minutes after each injection and, by placing him in the proper position, to prevent the falling backward of the tongue. When the patient fell asleep after the injection his temperature, respiration, and blood pressure returned to normal. It took longer for the pulse to become normal. The intramuscular injection of 1 Gm. of pentobarbital combined with the vitamins B_1 and B_{12} sometimes prevented the onset of delirium. Treatment was continued for several days. Of 40 patients who received preventive treatment 6 developed a mild delirium, but all recovered. Of eight who were treated for true delirium, all recovered without sequelae.

GERMANY

Absorption from the Small Intestine.—U. Ritter of Berlin (*Medizinische*, no. 10, p. 406, 1959) stated that isotope techniques have provided reliable means for estimating absorption and transport of fat in the small intestine. Labeled linoleic, palmitic, or stearic acid and tagged muscle fats, triolein, or oleic acid were used. The studies confirmed the belief that higher fatty acids are almost completely carried away in the lymphatics. In quantitative estimations of the amount of fat in the feces, 10% of the fat ingested was considered normal. After gastric resection an increased excretion of fat, especially of bacterial fat, was regularly found. In patients with ileitis delayed and decreased absorption of fat was found in addition to an increase of oleic acid in the stool. Fat absorption was delayed and decreased also in patients with carcinoma of the head of the pancreas. Biliary acid and pancreatic juice are no longer considered so important in the absorption of fat. Fat may be absorbed in their absence. Studies with tagged yeast protein showed that protein is mainly absorbed in the jejunum.

It was found that less than 10% of the iron contained in the food is absorbed, but the absorption rate is increased in patients with anemia. Absorption of vitamin A depends on various factors. Calcium absorption in the ileum was improved by administering vitamin D. Absorption of vitamin K required the presence of bile. The importance of the vitamin B complex in the utilization of food was confirmed further. The absorption of vitamin B_{12} was reduced in general disturbances of absorption.

Changes in Tuberculosis.—F. G. Schmidt (*Beitr. Klin. Tuberk.* 121:42-48, 1959) reported that marked changes in the manifestations of tuberculosis are occurring. Tuberculous cavitation now proceeds without noticeable symptoms. Highly inflammatory, exudative-caseous tuberculosis has become rare. The decrease in laryngeal and intestinal tuberculosis is believed to have resulted from chemotherapy. Bronchial tuberculosis has been regressing. On the other hand, the number of lower lobe infections and tuberculomas is increasing. In tuberculomas isoniazid probably enters the granules but there meets a quiescent and therefore invulnerable bacterial flora. This does not follow treatment with streptomycin, thiosemicarbazone, and para-aminosalicylic acid. In patients with tuberculous cavities even if the healing process has not been changed by chemotherapy, it is accelerated and the therapeutic results probably last longer.

Extrapulmonary Tuberculosis.—J. Kastert (*Beitr. Klin. Tuberk.* 121:61-75, 1959) stated that chronic tuberculosis of the cervical lymph nodes with extensive scar formation and fistulas is more rare than in the preantibiotic era. This is not so much a result of chemotherapy as of early diagnosis. Intestinal tuberculosis is decreasing. Only intestinal obstruction has remained an indication for operation. Peritoneal tuberculosis has become rare, and the incidence of mesenteric lymph node infection is steadily decreasing. The incidence of skeletal tuberculosis has been the same for 10 years. Chemotherapy has reduced the danger of abscess and fistula formation in tuberculous spondylitis. There is a predominance of hyperplastic changes after specific joint or bone processes, while previously hypoplastic processes predominated.

Scrofula.—E. Brügger (*Beitr. Klin. Tuberk.* 121:244-245, 1959) stated that until 1949 he resected only the softened and fistulating tuberculous cervical lymph nodes, but since the end of 1949 he has resected all nodes larger than a small cherry with or without calcium deposits. Smaller nodes were excised when they showed a tendency to progress. Between 1950 and 1956, 1,016 patients with such nodes had radical resections. The duration of treatment was comparatively short (about three months) and the number of relapses was low in this series. An inquiry among 300 patients five years after operation showed 3% with relapses and 1.7% with new infections. None of the patients operated on later developed lupus. All were given chemotherapy postoperatively in addition to general treatment. Surgical treatment obviated the need for radiotherapy.

Postoperative Gangrene.—Schuermann and Hornstein of Bonn (*Chirurg* [no. 8] 30:371, 1959) said that postoperative gangrene is not frequent but is alarming because of the great pain it causes, its steady progression, its resistance to treatment, and the death rate of about 30%. The average duration is about eight months. Circumferential incision is recommended. The authors used corticosteroids instead of antibiotics for treatment. They reported excellent results with the oral use of prednisone.

Actinomycosis.—A. M. Walter (*Deutsche med. Wchnschr.* [no. 32] 84:1421, 1959) stated that when diagnosed early actinomycosis should be treated with large doses of combined chemotherapy for 6 to 12 weeks. A combination of general and local chemotherapy together with surgery should always be considered, but its use should depend on the stage of disease and location of foci. Careful follow-up examination is necessary to detect relapses and delayed metastases. The author recommended a mixture of sulfonamides; penicillin in doses of 1 to 6 million units a day; 1.5 to 2 Gm. of tetracycline daily by mouth; 2 to 2.5 Gm. of chloramphenicol daily; 1 to 2 Gm. of streptomycin a day intramuscularly; or erythromycin and oleandomycin in daily doses of 1.2 to 1.6 Gm. orally. Penicillin and sulfonamides may be used locally. For the treatment of oropharyngeal actinomycosis, benzoquinone, guanylhydrazone, thiosemicarbazone, and large doses of prednisolone were recommended.

Cause of Pneumonia.—H. Fischer of Berlin (*Ztschr. ges. inn. Med.* [no. 13] 14:648, 1959) reported that pneumococci no longer play the predominant role as the cause of pneumonia. He examined the sputum of 26 patients with lobar and 24 with lobular pneumonia before the patients had been given any treatment. Streptococcus viridans predominated followed by Escherichia coli and staphylococci. In each patient the same micro-organisms were found in the sputum and in the pleural exudate. Treatment was directed specifically against the organism identified.

Progressive Scleroderma.—E. Nägele of Giessen (*Klin. Wchnschr.* [no. 13] 37:697, 1959) stated that some conditions such as disseminated lupus erythematosus, dermatomyositis, and progressive scleroderma that were previously thought to be skin diseases are cutaneous manifestations of systemic diseases. Scleroderma occurs in a disseminated and in a harmless circumscribed form which is confined to the skin and is also referred to as sclerodactyly or acrosclerosis. In progressive scleroderma the esophagus is frequently transformed into a rigid tube without peristalsis. The patients complain of difficulty in swallowing and a feeling of pressure in the epigastrium and must wash down every mouthful of food with liquids. Esophageal ulcers may occur.

Similar changes may affect the whole gastrointestinal tract and cause pain, ileus, sprue-like diarrhea, and tarry stools. Histological examinations show that muscular tissue in the digestive tract is replaced by connective tissue, but there is probably also disturbance of the intramural nervous plexuses which decreases peristalsis. There may also be signs of progressive myocardial fibrosis, usually attended by cardiac dilatation. Nodules and cell aggregates resembling Aschoff's nodules are found on histological examination. The clinical diagnosis of sclerodermatic myocardial changes is difficult. The electrocardiogram may show arrhythmia, broadening of the QRS complex, or low voltage. Medium-sized arteries may show proliferating endarteritis, and the small arteries and arterioles may show fibrinoid intimal damage.

Pulmonary fibrosis occurs mainly in the lower lobes. Histological examination of the lungs shows an increase of interstitial tissue and cyst formation, which in some cases resembles bronchial dilatation and in some emphysematous vesicles. Endarteritic vascular changes are also found in the lungs. Renal involvement causing increased blood pressure and abnormal findings on urinalysis is always an indication of the terminal stage. The kidneys show the signs of chronic nephritis with thickening of Bowman's capsules and hyalinization of the capillary loops, as in malignant sclerosis. The endocrine glands may be involved. Joints are often stiff and contracted because of capsular shrinkage. Osteolysis in the terminal phalanges and calcification of soft tissues and internal organs are characteristic. The serum calcium level is often raised. ACTH and cortisone are the most effective therapeutic agents, although their effect may be transitory. Antibiotics are indicated, especially in patients with pulmonary fibrosis and inflammatory signs. Appropriate skin care, respiratory exercises, and massages are important. The average duration of the disease is seven years.

Prednisone and Phenylbutazone.—K. Dziuba (*Medizinische*, no. 38, p. 1768, 1959) obtained good results with a combination of 50 mg. of phenylbutazone and 1.25 mg. of prednisone in a series of 210 patients. The dosage (four to nine of the combined tablets daily) depended on the type and severity of the disease. After five days the dosage was reduced to two to six tablets daily. The duration of treatment varied. One group of patients, in particular those having rheumatoid arthritis, osteoarthritis, or spondyloarthrosis, were referred to their family physicians for further treatment with a minimal maintenance dosage. For a trial the combination was given to 27 patients with thrombophlebitis and 9 with skeletal metastases.

In the whole series 135 patients had been treated unsuccessfully with other drugs. Criteria for successful treatment were subsidence of pain, local inflammation, swelling, fever if there was any, and improved mobility. Inflammation, swelling, pain, and fever were promptly relieved. Results were excellent in those with rheumatic diseases and thrombophlebitis. Most patients with osteoarthritis, spondyloarthrosis, and affections of intervertebral disks with brachialgia, sciatic neuralgia, and lumbago responded well. Surprising results were seen in four patients with rheumatic endocarditis and one with myocarditis who had been treated with antibiotics, sulfonamides, pyrazole, and aminophenazone derivatives for prolonged periods. Three promptly became afebrile, the sedimentation rate declined, and leukocytosis and subjective symptoms improved. In the other two the effect occurred more slowly.

Interruption of the treatment resulted in spontaneous relapses in two patients, but these were controlled by renewed administration of the preparation. The results were excellent in the patients with acute thrombophlebitis, but only one patient with skeletal metastases became free of pain within 48 hours. Results were excellent in 105 patients, good in 50, and fair in 26; 29 patients were not benefited. The preparation was well tolerated, even when large initial doses were given. No major side-effects were seen. Only two patients had to discontinue treatment because of gastric intolerance. Because of these good results the preparation is recommended, in particular, for continuous treatment of chronic diseases.

Pemphigus Vulgaris.—E. Schlotter (*Hautarzt* 10:173, 1959) gave corticosteroids to 20 patients with pemphigus vulgaris. The initial dose depended on the severity of the disease and localization of the cutaneous or mucosal changes. The prognosis is most favorable when there is no mucosal involvement. Larger doses are required when the skin lesions have spread to the mucosa. In patients with pemphigus vulgaris confined to the skin, remission was achieved with total doses of 500 units of ACTH, 900 mg. of cortisone, or 860 mg. of prednisolone. In those with secondary spread to, or changes of, mucous membranes the doses were 1.80 to 4.15 Gm. of cortisone or 1.135 to 2.380 Gm. of prednisolone. Large single and total doses were required when the primary lesions were mucosal, when they remained localized, or when they secondarily affected the skin. One patient who had frequent severe exacerbations became symptom-free on maintenance doses of 150 mg. of prednisone daily.

Undesirable side-effects were nephrosis (present before treatment), increase of blood sugar level, moon face, and obesity of the trunk. These were treated appropriately, and it was not necessary to discontinue hormonal therapy. Prednisone proved generally valuable. Corticosteroids promptly achieve a remission of the acute activation, but use of hormones is not a specific treatment for pemphigus vulgaris. Four patients had relapses, but these responded to further treatment with corticosteroids. In this series 15 of the patients were alive and 12 of them were free from skin symptoms when last seen, some with and some without a maintenance dose. The duration of freedom from symptoms was two months to four years.

Asphyxia Neonatorum.—A. Braun and A. Mann (*Arch. Kinderh.* 159:130, 1959) said that cerebral, pulmonary, and cardiac forms of asphyxia neonatorum occur. Only few, and sometimes contradictory, reports are available on the pulmonary form. Hyalin-like membranes were found in 63 of 202 neonates (34 full term and 188 premature) who died within the first week of life. No hyalin-like membranes were found in a series of 37 stillborn infants. Hyalin-like membranes occurred in 56 of the premature infants and 7 of those born at full term. It is thought that the hyalin-like membrane develops from the exudation of blood components in the septums and alveolae of the lungs, as it is mainly seen in premature infants, and that it dries up and is reabsorbed. The membranes may contain cellular material and fat plugs. In the course of increasing blocking of gas exchange, latent anoxia develops and eventually causes the premature infant's death, but the prognosis is not invariably hopeless. Neonates have survived even severe symptoms and recovered within a comparatively short time. No specific treatment is known.

Multiple Sclerosis.—D. Ploog and co-workers (*Klin. Wchnschr.* 37:946, no. 18, 1959) treated a series of 30 patients who had multiple sclerosis with prednisolone. They used short-term massive courses of treatment, expecting a more distinct prednisolone effect than with the common continuous treatment and better differentiation between therapeutic results and spontaneous remissions. They gave 60 mg. for 2 days, 90 mg. on the 3rd and 4th day, then reduced the dose by 5 mg. every 2nd day and completely withdrew the drug on the 14th day. About half of the patients were given ACTH after prednisolone treatment. Neurological examination and, whenever possible, examinations of the spinal fluid were made after each phase of prednisolone treatment. The number of courses depended on the success of treatment, occurrence of complications, etc.

Response to treatment was evident in 63% of patients with acute, 56% of patients with intermittent, and 35% of patients with chronic progressive forms of the disease. Symptoms were favorably influenced in the following order of frequency: bladder and rectum disturbances, subjective symptoms, spinal fluid changes, sensory and coordinative disturbances, reflex anomalies, ocular changes, and cranial nerve deficiencies. Optic nerve atrophy was irreversible. In 15 patients the spinal fluid showed a reduction in the number of cells and total protein. There was no fixed relationship between degree of improvement and number of prednisolone courses given, but chronic forms were not essentially improved when this effect did not become apparent after the first course.

Side-effects were usually mild euphoria, restlessness, and occasionally an alteration of the sleeping-waking rhythm. More serious side-effects (appendical irritation in two and activation of previous inflammatory processes in two) occurred. One adolescent patient had a mild pituitary basophilism after the third course. Comparing the prednisolone-treated patients with a group of 30 who were given retroplacental serum, the author concluded that improvement was generally greater in the first group. It was concluded that prednisolone as used in this series was at least as effective as the usual treatments and clearly superior for treating patients with acute forms.

Erythroblastosis Fetalis.—G. Essigke of Jena (*Monatsschr. Kinderh.* 107:1-5, 1959) tested the excretory capacity of the liver for sulfobromophthalein in 29 infants who had erythroblastosis fetalis and who had been given exchange transfusions. The half life of the dye in the serum was markedly above normal. Normal liver function was not reached until the fourth week. In infants with this disease who had not been given an exchange transfusion, normal liver function was not achieved until the sixth week. The half-life values were also prolonged in healthy neonates, but in these normal values appeared within two weeks. The studies showed that in erythroblastotic infants hemolysis and hepatic insufficiency are independent of each other and are of different degrees. True liver damage occurs in erythroblastotic infants. It consists mainly in a disturbance of permeability and hypoxia, both due to an antigen-antibody reaction.

Renal Function Test.—H. Mühlan (*Ztschr. Kinderh.* 82:40-43, 1959) estimated the phenol red excretion for a renal function test, according to the method of Stave, in 57 children with healthy and 21 children with diseased kidneys. Since the values obtained at 15 and 30 minutes were scattered within a wide margin, the author recommended evaluation of the excretion at 60 minutes. In healthy children the amount of phenol red excretion averaged 60%. Values below 55% were considered pathological. These results were in fair agreement with those obtained by Zapp. In healthy infants in the second month of life excretion was markedly below later readings, but by the third month excretion approached the normal average. Excretory values were usually lowered in children with disease of the kidneys or urinary passages.

Metabolism of Vitamin D.—O. Hövels and D. Reiss (*Ergebn. inn. Med. u. Kinderh.* 11:206-263, 1959) stated that the intake of adequate amounts of protein and fat is necessary for good calcium absorption. An absorption-promoting effect of vitamin D is found in patients with rickets but not in healthy children. The vitamin has only a slight effect on constitutionally poor calcium utilization. A direct effect of the vitamin on phosphate absorption is doubted. Vitamin D increases calcium excretion even if serum calcium levels are not raised, since the inhibition of tubular reabsorption alters the calcium clearance rate. In rickets caused by vitamin D deficiency the phosphate clearance is increased but returns to normal after administration of vitamin D. Phosphate clearance is not raised in rachitogenic tetany but is increased after ingestion of vitamin D.

In vitamin D resistant rickets phosphate clearance is raised because of disturbance of tubular reabsorption and can be improved by daily doses of 100,000 to 800,000 units daily. The clearance is markedly raised and causes the characteristic hypophosphatemia in patients with hyperparathyroidism. Vitamin D lowers the increased phosphate clearance and in patients with hypoparathyroidism it causes the reduced phosphate excretion to increase. It has no effect on phosphate clearance in healthy subjects. Reduced tubular reabsorption of amino acids is a specific indication of vitamin D deficiency. Aminoaceturia subsides within three to eight weeks after administration of vitamin D. Of two groups of children with equal intestinal calcium absorption, the one receiving the larger amount of vitamin D showed the greater improvement in growth.

Dexamethasone.—Scheiffahrt and Zicha (*Medizinische*, no. 38, p. 1737, 1959) stated that the marked side-effects of cortisone and hydrocortisone prompted the search for new but related substances. Triamcinolone was developed by the introduction of a fluorine atom and hexadecardrol and dexamethasone by methylation. Since the latter proved markedly superior to other glucocorticoids in animal experiments, the authors gave it to 130 patients for whom corticoid treatment was indicated. The initial doses were 5 to 10 mg. daily by mouth; after two or three days the dosage was reduced by 0.5 mg. every other day. Patients with acute diseases were treated for two or three weeks, but in those with such chronic diseases as nephrosis, Hodgkin's disease, and hemolytic syndromes treatment was continued for up to 120 days with a total dose up to 320 mg. The maintenance dosage was 1 to 2 mg. daily.

Therapeutic successes depended on the type of disease and on the dose. In patients with rheumatic diseases, acute hepatic disorders, and hemolytic syndromes, success was apparent after 12 to 24 hours. The effect in patients with ulcerative colitis was similar to that of prednisolone. The preparation was least effective in patients with acute bronchial asthma, who responded best to derivatives for intravenous injection. In all patients with chronic nephritis and nephrosis, satisfactory diuresis set in and the subjective condition improved, but protein excretion was improved in only a few patients and only temporarily. The best effect of dexamethasone was seen in patients with active rheumatic processes. Dexamethasone and triamcinolone treatment did not effect the serum sodium level even in long-term treatment with large doses. The serum potassium level and potassium excretion at first remained unchanged, but after prolonged treatment a slight decrease of serum potassium and an increase of potassium excretion occurred.

Calcium, on the other hand, was mobilized more promptly. The excretion more than doubled, and the serum level declined below normal after four weeks at the latest. The results for organic phosphate in serum and urine were similar. Two patients being treated for a prolonged period developed osteoporosis. It was therefore recommended that in long-term treatment protein-anabolic hormones be given. The diuretic effect of dexamethasone was marked and usually set in after three to five days. While the neutral 17-ketosteroid excretion decreased after 30 days of corticoid treatment, corticoid excretion was significantly reduced after only a few days and decreased still further as treatment continued. Other hormonal effects occurred only with prolonged use of large doses. Eosinophil counts were checked in few patients and were found to return to normal in patients in whom they were previously extremely high.

Dexamethasone had less diabetogenic effect than did prednisolone and triamcinolone. Only 1 of 10 diabetic patients required an increase of the insulin dose by 8 units daily. The others, including those taking sulfonyl carbamide, showed no essential changes. Triamcinolone, on the other hand, in some patients caused a marked deterioration of glucose metabolism. Dexamethasone caused a greater catabolic effect than did prednisolone. The usual gastrointestinal side-effects were seen with dexamethasone, but only one patient who had neither an ulcer nor hyperacidity had marked gastrointestinal symptoms. Best tolerated by the stomach was 6-methylprednisolone. In one patient silicotuberculosis of long standing was activated by steroid treatment. Dexamethasone should be reserved for hospital treatment, in view of its possible side-effects. Long-term treatment with large doses may require antibiotic prophylaxis and antacids. For the termination of treatment depot-ACTH should be given for at least two days.

Cortisone and ACTH for Infections in Children.—D. Palitzsch (*München. med. Wchnschr.* **101**:241-246, 1959) treated 1,000 children who had severe infections with cortisone and ACTH. Cortisone inhibits eosinophils, lymphocytes, plasma cells, phagocytosis, toxic proteolysis, synthesis of hyaluronic acid, hyaluronidase, permeability, migration of leukocytes, antibody formation, fibroblasts, sprouting of capillaries, and scar formation. It promotes maturation of neutrophils, reticulocytes, thrombocytes, protein decomposition, thickening and polymerization of the ground substance, sealing of vessels, and vascular tone. Most diseases from infections require simultaneous antibiotic treatment. Special attention should always be paid to the disturbance of antibody formation by steroids. Short-term treatment in which large initial doses are administered before the dosage is gradually decreased is generally to be preferred. The indications now recognized include emergency treatment of Waterhouse-Friedrichsen syndrome, severe acute encephalopathy, and highly toxic conditions in infants and small children; resistant infections; hyperergic infections; and antibiotic-chemotherapeutic allergy. Cortisone is preferred in severe infections since these are associated with temporary blocking of adrenocortical function. The dosage depends less on age than on the severity of the infection. Short-term treatment is almost free of dangers even with large doses.

With long-term treatment the nitrogen losses in cortisone treatment (negative nitrogen balance and increased proteolysis) and sodium chloride water retention and potassium losses (severe potassium losses lead to energetic-dynamic heart failure) must be borne in mind. Intrathecal treatment of purulent meningitis with 5 to 10 mg. of hydrocortisone every other day counteracted the development of hydrocephalus by virtue of inhibiting mesenchymal proliferation. Steroid treatment proved valuable against staphylococcic sepsis, abscess-forming pneumonia in infants and small children, pleural empyema, bacterial enteric infections, tuberculosis including tuberculous meningitis, hemorrhagic measles, measles encephalitis, meningoencephalitis in smallpox and mumps, mumps orchitis, severe hepatitis, and infectious mononucleosis.

Tri-iodo-thyronine.—Knorr and Freislederer of Munich U. (*München. med. Wchnschr.* 101:718-723, 767-769, 1959) reported a series of 50 hypothyroidal children treated with tri-iodo-thyronine. Improvement occurred promptly. Sclerosis of the base of the skull in myxedema regressed in 17 months, cretinistic hips in 21 months. The margin between the therapeutic and toxic dose is greater than that of the dried gland. Cumulative effects were rare. Good results were achieved in some patients with obesity, nephrotic syndrome, nervous anorexia, dwarfism, and goiter of puberty.

Strophanthin and Cardiac Infarction.—Anschütz and Toker (*Ärztl. Wchnschr.* 14:609, 1959) noted that Edens highly recommended strophanthin for cardiac infarction. Other authors strongly advised against this treatment, and a third group recommended strophanthin only for patients with cardiac failure. Between 1953 and 1958 the authors gave strophanthin to every other patient with cardiac infarct. All patients also rested in bed and were given a salt-free diet, oxygen, analgesics, and sedatives. The dose of strophanthin was 0.625 mg. twice daily or 1.25 mg. once daily. Of 53 patients treated with strophanthin 20 died during their stay in hospital and 33 were discharged after six weeks of strict bed rest. Of the 53 controls 17 died and 36 were discharged. A total of 31 patients had signs of cardiac failure after the infarction, which usually occurred on the second and fourth day in the form of tachypnea and symptoms of congestion; 20 of these patients were treated with strophanthin, and 8 died in the first week. Of the eight patients three had not been given strophanthin. Although the number of patients was too small to permit valid conclusions, the results suggested that the prospects of surviving cardiac failure in infarction are not changed by strophanthin.

Long-Acting Sulfonamide for Children.—Schönfeld and Sommerfeld (*Ärztl. Wchnschr.* 14:619, 1959) reported that 2,4-dimethoxy-6-sulfanilamido-1,3 diazine is especially suited for the treatment of bacterial infections of children, since it is the only long-acting sulfonamide available in solution. Children prefer to take drops, and it is easier to add flavor to drops. Since the half-life of this drug in serum is about 40 hours, one dose a day is sufficient. The recommended dosage for infants and small children is 10 mg. per kilogram of body weight after an initial dose of twice that amount. In severe infections in children there are no disadvantages in doubling the dose. Infants and small children were always given the preparation in the form of drops, but older children may be given tablets. A series of 120 patients who had bronchopneumonia, bronchitis, tonsillitis, otitis media, lymphadenitis, gastroenteritis, dysentery, and enteritis, all associated with a high fever, were treated with the drug. In two patients with bronchopneumonia and two with otitis media the response was poor, and they were given antibiotics. None of the patients lost appetite; no blood and urine changes were observed; and no allergic skin reactions or renal impairment was noted. The preparation was highly effective and well tolerated.

Hydroxydione Anesthesia.—J. E. Rollenhagen (*Deutsches. med. J.* [no. 9] 10:310, 1959) stated that hydroxydione has proved a valuable basic anesthetic for elderly patients in whom cardiac or circulatory complications are to be expected. It has hypnotic action. The patients sleep quietly, as in normal sleep, but sleep is induced more slowly and evenly than with barbiturates. Increasing the dose prolongs but does not strengthen the effect. Combination with barbiturates is contraindicated since the combination increases the danger of respiratory depression. The substance can be used in patients with hepatic and renal disorders. Cytochrome C and cocarboxylase are antidotes.

Hydroxydione is indicated in patients with cardiac and circulatory insufficiency, diabetes, ileus, and peritonitis. Since the product is partly broken down in the liver and is excreted through the kidneys, careful dosing is necessary in patients with renal and hepatic conditions. Hydroxydione is best given in a 2% procaine solution with a 10% isotonic sodium chloride solution as a solvent. Premedication with meperidine, atropine, or promethazine and an antihistaminic is recommended. Since hydroxydione is used only as a basic anesthetic, anesthesia is continued with ether or nitrous oxide. The patients usually awaken soon after the operation and then often sleep for another two to three hours. When this drug is used requirements for analgesics in the first 12 to 24 hours are greatly reduced.

Chronic Rheumatic Disease.—W. Grab of Giessen (*Therap. Gegenw.* 98:323, 1959) stated that mesenchymal connective tissue plays an important role in rheumatic diseases. With increasing age there is a decrease of ground substance and an increase of fibers. All inflammatory reactions take place in the ground substance and are always elicited by chemical agents which activate extracellular enzymes, in particular hyaluronidase. The latter reduces or depolymerizes the large molecules of the ground substance to smaller molecules. Cortisone inhibits this process and thus exerts a nonspecific antirheumatic action. This explains the reactivation of rheumatic processes when such treatment is discontinued. Reactivation can be prevented by prolonging administration. The inflammation then has time to heal. Prednisolone, whose antiphlogistic action is 5 to 30 times greater than that of cortisone, does not have the side-effects of the latter. All adrenocortical hormones, however, increase the degradation of proteins and mineral deprivation. This leads to osteoporosis, which can be suppressed by giving sex hormones. Treatment must never be stopped abruptly, since this would cause atrophy of the adrenal cortex. Dosages should be gradually decreased and ACTH prescribed to bridge the withdrawal period.

Salicylates are more effective in the acute than in the chronic phase, and their use in rheumatic conditions is still justified. Aspirin (4 to 6 Gm. daily) is effective, and aminopyrine has proved valuable. Phenylbutazone has been widely used, but it may damage the bone marrow, affect blood coagulation, and cause allergic reactions and giddiness. Radioactive gold is comparatively harmless. Chloroquine has an indirect antirheumatic action which becomes manifest only after a comparatively long latent period.

Chlorpromazine and Shock for Chronic Psychoses.—R. Vosseler (*Med. Monatsschr.* [no. 5] 13:284, 1959) treated a series of 50 patients who had chronic schizophrenia with a combination of convulsive treatment and chlorpromazine. The patients had been treated for at least one year by the usual methods without success in a mental hospital. For eight days prior to the combined treatment the patients were given 150 to 200 mg. of chlorpromazine by mouth daily. They were then given electroshock in the evening for four days in addition to 100 mg. of chlorpromazine daily for three to four weeks. No side-effects from the chlorpromazine were observed. To obtain lasting improvement the patients were given three such courses of treatment over a period of about eight months.

The combination of additional chlorpromazine and electroshock in the evening (with the use of the natural requirement for sleep) freed the patients of shock fear. A short-acting anesthetic was not required, and instead the patients were given 50 mg. of chlorpromazine intravenously or intramuscularly in the terminal stupor. The next morning they woke up refreshed and did not remember the happenings of the previous night. After three shock treatments they could usually be admitted to occupational therapy. After conclusion of the combined treatment, 14 women were discharged improved. They were free from hallucinations and in a balanced state of mind, but four of them had to be readmitted after three months. Nevertheless, one could not consider the treatment to have failed in these or in the other 36 patients since all of them were markedly improved and some of them could be admitted to occupational therapy for the first time in several years of hospitalization.

Thrombosis from Chlorpromazine and Reserpine Treatment.—Grahmann and Suchenwirth (*Nervenarzt.* [no. 5] 30:224, 1959) stated that no references to thrombotic complications were found in the literature on the use of chlorpromazine or reserpine. Because of an impression that thrombotic processes occurred more frequently in psychiatric patients treated with the above-mentioned drugs than in those having other treatment, they studied a series of 338 courses of 100 to 500 mg. daily of chlorpromazine and 60 courses of 3 to 12 mg. daily of reserpine. In only a few patients were the drugs combined. The patients were suffering from endogenous schizophrenia and cyclothymia. The results were compared with those in 464 psychiatric patients who were treated with insulin, electroshock, nonspecific sedatives, and hypnotics.

Thrombosis developed in 11 in the group treated with chlorpromazine and in 2 of those treated with reserpine but in only 2 in the control group. This indicated a clear-cut tendency to thrombosis in patients treated with chlorpromazine and reserpine. No such tendency has been observed in patients undergoing other treatments. Thrombophlebitis occurred especially in those who were severely agitated and needed heavy sedation. Two deaths from pulmonary embolism occurred in patients who were agitated and depressed. The greater tendency to thrombosis in patients treated with chlorpromazine and reserpine might be due to damage of the vascular wall, an influence on the coagulation system, and stasis of the venous circulation, the latter being the most important factor. Countermeasures advised for endangered patients are regular massage of the legs, getting up for a brief period daily, and administration of anticoagulants.

INDIA

Conference on Leprosy.—At the Seventh All-India Leprosy Workers' Conference, held in Bombay in December, the Union Health Minister said that by the end of the third five-year plan the government hoped to cover the whole country with facilities for treatment of this disease, which at present is as widely prevalent as tuberculosis. The governor deplored the lack of sympathy from the public for those affected with leprosy. There is an urgent need for realization on the part of the public that leprosy is a curable disease. Family and social boycott of lepers does not lead to the cure or the eradication of the disease. The president of the conference said that about 1,500,000 lepers are found in India, or more than half of the world's total number of lepers. He urged that leprosy control and eradication be treated as a national problem and that control measures be supported by the people and the government.

Citicide.—Citicide, a pesticide that is much more efficient than DDT and less costly, has been developed in the regional research laboratory in Hyderabad. The raw materials used in this product are chlorine and turpentine, both of which are plentiful. Tests have shown citicide to be highly toxic to a wide variety of pests.

Medical Education.—Addressing the 52nd session of the Medical Council of India, C. S. Patel (*Antiseptic,* vol. 56, Dec., 1959) said that the shortage in the number of physicians even at the end of the second five-year plan period is estimated to be not less than 10,000. In spite of the fact that a number of medical colleges have been started in different parts of the country in recent years, it will be some time before all of them are able to take all the students they have planned for. Even then it is feared that their full number of students will not provide the number of doctors the country needs. It is expected that there will be a total pool of about 80,000 trained graduates in medicine by the school year 1960-1961, if about 2,500 doctors graduate each year. One way of overcoming the shortage would be to expand the capacity of the existing colleges by 25 to 30%, particularly in areas where there are few colleges. Most of the existing colleges are prepared to undertake such an expansion provided they receive financial assistance. It is, however, necessary to ensure that quality is not sacrificed in an attempt to secure a quantitative expansion.

Furazolidone.—A. Massa (*Antiseptic,* vol. 66, Dec., 1959) used furazolidone in the treatment of a series of 71 patients who had acute and chronic intestinal infections. The dosage for adults was 100 mg. four times a day for 6 to 12 days. The patients were considered cured when pathogenic bacilli disappeared from the stools. The pathogens isolated from different patients were Shigella in 8, Salmonella in 16, Entamoeba histolytica in 5, Proteus in 4, and Escherichia coli and Staphylococcus aureus in 12, while 26 suffered from nonspecific diarrhea. After treatment, the pathogens were eradicated and clinical cure obtained in all but two patients with shigellosis, two with salmonellosis, and one infected with Esch. coli and Staph. aureus. Some patients who had proved resistant to antibiotics such as tetracycline, chloramphenicol, and streptomycin responded to furazolidone readily and were cured.

The drug was found to be effective not only in patients infected with a single bacterial species but also in those with mixed infections. All the patients with acute amebic dystentery responded well to the new drug, and follow-up studies revealed absence of any recurrence of infection. Similarly, the group of 26 patients with nonspecific diarrhea showed good results. The attack usually lasted for 24 to 48 hours, while in untreated patients the presence of Salmonella organisms could be demonstrated for 7 to 12 days. Thus bacteriological and clinical cure was obtained in more than 85% of the treated patients. The results were consistent and much superior to those obtained with antibiotics and sulfonamides. The drug was found to be safe and effective even in infants and pregnant women. No cumulative effect was observed. The incidence of unfavorable side-reactions was negligible. A few patients complained of nausea, but the drug therapy did not have to be discontinued in any patient. The drug would be of value in intestinal infection in places where laboratory facilities are lacking or in treating patients with acute cases where delaying treatment till the laboratory reports arrive is undesirable.

NETHERLANDS

Pheochromocytoma.—M. Smits (Thesis, University of Utrecht, 1959) studied the family (39 persons) of a patient with a pheochromocytoma. In the infants and children (17 persons) his examination was limited to the history and the physical examination. The examination of the adults included in addition a glucose-tolerance test, histamine test, and determination of catacholamine excretion in the urine. Four members of this family appeared to have a pheochromocytoma, and in 10 of the deceased members such a diagnosis was likely. This is the ninth family which has been described in which inherited pheochromocytoma occurs. Of the present family, four of the deceased members had diabetes and three of these probably had a pheochromocytoma. Eight members of this family had an enlarged thyroid gland and one of these had a pheochromocytoma. In five of the deceased women of this family, pregnancy had been complicated by an eclampsia-like syndrome. All these women had a pheochromocytoma.

The relationship between pheochromocytoma and diabetes or enlargement of the thyroid gland remained obscure. The simultaneous occurrence of an eclampsia-like syndrome and pheochromocytoma suggested a definite relationship in the pathogenesis of both diseases. Some authors have observed certain differences between true eclampsia and eclampsia in patients with a pheochromocytoma. No marked difference in the excretion of catacholamines could be demonstrated between the members of the present family and a control group of equal number. The results of the present investigation and the reports of earlier observers led the author to conclude that the mode of inheritance of pleochromocytoma is monomeric, dominant, and autosomal, with variable expression in the phenotype.

NORWAY

Pleuropulmonary Manifestations in Lupus Erythematosus.—Jon R. Myhre (*Acta med. scandinav.* 165:55-60, 1959) stated that pleuropulmonary manifestations occurred in 16 of a series of 18 patients with systemic lupus erythematosus. In 10 the changes were bilateral when first demonstrated, and, with one exception, bilateral changes developed in the others. The pleuropulmonary affection often appeared months or years after the onset of the disease but could not be considered a preterminal or terminal event. It might be the first local manifestation of the malady. In the basal portion of the lung uneven and ill-defined opacities of varying size and density appeared together with a pleural effusion of small or moderate size. The diaphragm tended to rise, and the elevation was often unusually marked in proportion to the pleuropulmonary changes. Plate-shaped shadows of the type usually considered to be of an atelectatic nature tended to develop in the basal lung field.

On improvement the diaphragmatic elevation generally persisted much as before. Though the separate components of the pleuropulmonary manifestations in lupus erythematosus were nonspecific, together they constituted a clinicoroentgenologic syndrome that might be more characteristic than was generally appreciated. After later observing another patient with pleuropulmonary lupus erythematosus who was wrongly assumed to have a subdiaphragmatic abscess, the author stated that lupus erythematosus should be included in the list of possibilities to be excluded before making a diagnosis of subdiaphragmatic abscess in obscure cases.

UNITED KINGDOM

Home on the Second Day.—It is the practice at St. Luke's Maternity Hospital, Bradford, to examine weekly, from the 24th week of pregnancy onward, women who have shown abnormalities in previous pregnancies. The main object is early detection and hospitalization of those with hypertension. With a fixed number of beds, however, the hospitalization of these patients could be achieved only by reducing the number of lying-in beds. It was, therefore, decided as an experiment to send home on the second day of the puerperium 25% of the mothers who had their confinement in the hospital.

During the first year of the experiment, 741 women were sent home on the second day under the care of their family doctors and domiciliary midwives. None of the 741 babies died during the first 14 days of life, and it was necessary to hospitalize only 4 of them. Only three mothers were readmitted to hospital, two because of secondary postpartum hemorrhage and one because of pyrexia. Dr. G. Theobald, department head, stated that sending the mothers home on the second day, besides making beds available for urgent cases, prevented the babies from becoming a culture medium for antibiotic-resistant staphylococci so prevalent in hospitals.

Control of Anticoagulant Therapy.—Long-term anticoagulant therapy is being given to an increasing number of patients who have had a myocardial infarction or recurrent arterial or venous thrombosis. The methods of control vary from laboratory to laboratory. If anticoagulant therapy and prophylaxis are to become recognized practice, a standardized and easily performed procedure for determining the coagulability of the blood is essential. Matthews and Walker (*Lancet* 2:1159, 1959) tried the thrombotest introduced by Owren of Norway. This is designed to overcome the disadvantages of tests in current use, mainly the Quick prothrombin time and the prothrombin and proconvertin (P and P) method of Owren and Aas. Four clotting factors in blood are depressed by synthetic anticoagulants derived from coumarin, and only one of them is revealed by the Quick test and only two by the P and P test.

The new test reflects sensitively the reduction in all four factors, vitamin K deficiency, and liver disease. The reagent, which is now available commercially, contains a crude cephalin, which is a weak tissue thromboplastin made from horse brain, and normal plasma from which all the factors depressed by coumarin anticoagulants, but no others, have been removed. The preparation, which is stored in ampuls as a freeze-dried powder, may be stored for many months and is suitable for use with capillary or venous blood. The procedure is to add 0.1 ml. of whole blood to 0.5 ml. of reagent at 37 C and to observe the clotting time. The normal figure is 35 to 40 seconds. The result is expressed as a percentage of normal read from a correlation curve prepared from dilutions of pooled normal plasma. For any one batch of reagent such a curve is valid for any subsequent tests done with this batch. This makes it possible for the manufacturer to supply a correlation curve with each batch of material. The test is simple and reliable, giving clotting times that are reproducible within ±1 second. In routine laboratory work thrombotest is likely to become the procedure of choice in controlling anticoagulant therapy and in following the clotting defect in patients with liver diseases.

Bathing Beach Pollution.—Health officers of holiday resorts along the coasts of Britain have repeatedly reported the contamination of bathing beaches with sewage washed up by tides. An expert committee was set up by the Medical Research Council to investigate the possible hazards to the health of holiday makers from this cause. (Medical Research Council Memorandum 37, Her Majesty's Stationery Office, 1959). Thousands of samples of sea water from over 40 beaches were examined bacteriologically. The results showed that there is virtually no danger of contracting infectious diseases such as enteric fever or poliomyelitis from sea bathing. With the possible exception of a few esthetically revolting beaches, the risk to health of bathing in sewage-contaminated sea water can be ignored. Only one typhoid epidemic has been ascribed to sea bathing, and the circumstances were most unusual. No evidence could be found of an association between poliomyelitis and bathing in sewage-polluted river or sea water. An association between upper respiratory infection and diving is widely accepted, but this association is independent of the bacterial content of the water.

The report states that possibly a million or more salmonellae would have to be swallowed before clinical infection resulted. The isolation of small numbers of organisms therefore need not cause alarm, as many gallons of sea water would have to be consumed to produce an infection. The bathing histories of 150 children living by the sea who contracted poliomyelitis and the same number of controls matched for sex and age were compared. Of 94 patients with paralytic poliomyelitis, 23 bathed during the three weeks before the onset of infection. Among the controls 24 of 94 bathed in the same period. In the nonparalytic group 22 of 56 and 20 of the 56 controls, 20 had bathed. These findings suggest that surf bathing is not associated with poliomyelitis.

Ketosis and Obesity.—Kekwick and co-workers investigated the mechanisms underlying the resistance of fat people to ketosis (*Lancet* 2:1157, 1959). They found that this resistance does not depend on a higher rate of utilization or excretion of ketone bodies by the obese because, after the intravenous injection of sodium β-hydroxybutyrate, one of the ketone bodies found in urine, its rate of disappearance from the blood was the same in obese as in nonobese subjects. Both groups excreted about the same amount in the urine, which was less than 1% of the injected dose. The possibility that the rate of production of ketone bodies is less in the obese was investigated.

Attempt was made to produce ketosis in obese and nonobese subjects by giving them a diet providing 1,000 calories daily of which 90% were supplied in the form of fat. Fourteen obese subjects were able to take this diet for as long as required, whereas seven of eight nonobese subjects were compelled to abandon it by the fifth day because of symptoms referable to ketosis. The obese had a slower rise of blood ketone levels and their urinary excretion was lower than that of the nonobese. In the latter the development of ketonuria and ketosis was preceded by a fall in the fasting blood sugar level, whereas in the obese there was no such fall, or it was minimal.

The authors calculated that the diet provided insufficient carbohydrate to satisfy the needs of the nervous system. They believed that the minimum of 75 Gm. a day required by the brain alone was derived from the dietary fat of the subjects studied and that the obese may be able to turn fat into carbohydrate at a higher rate than the nonobese. This would explain their resistance to ketosis.

CORRESPONDENCE

CRANBERRIES, TURNIPS, AND GOITER

To the Editor:—The first issue of THE JOURNAL this year ushered in 1960 with a pleasantly amusing statement, on page 62, implying that a bit of thought might be helpful in the enactment of laws having to do with the addition of chemical compounds to foods or with the interpretation and enforcement of these laws. The choice of three examples was excellent: aminotriazole, an efficient weed killer and a good antithyroid compound which was detected in cranberries; charcoal, used to color candy; and diethylstilbestrol, used to make capons without a highly paid cockerel surgeon. I heartily agree that consumption of charcoal is unlikely to induce cancer and that we can all continue to eat our burned toast; I agree, too, that diethylstilbestrol, though used for one-quarter of a century and in millions of people, has given no suggestion of being carcinogenic, but I am no expert in these matters. The indictment of cranberries, however, (and perhaps other comestibles to come), because of trace contamination with the weed killer aminotriazole, which has caused such devastation in the cranberry industry, introduces a subject of great personal interest.

It is misleading to refer to an antithyroid compound such as aminotriazole as a carcinogen because this term brings to mind locally acting chronic irritants such as coal tar, which when painted on the skin of animals induces epidermoid carcinoma, and soot, which is more carcinogenic than charcoal, and induction of scrotal carcinoma in chimney sweeps—if such still abound. The so-called carcinogenic action of aminotriazole and related compounds in rats results entirely from the antithyroid effect. Synthesis of thyroid hormone is inhibited (Alexander: *J. Biol. Chem.* 234:148 [Jan.] 1959), profound hypothyroidism is induced, and thereby excessive secretion of thyrotropin from the pituitary is evoked. It is this intense thyrotropic stimulus that causes goiter and, if the stimulus is continued long enough, nodular goiter. These hyperplastic, friable, and vascular glands have sometimes been found associated with nodules of hyperplastic thyroid tissue in the lungs. The implication of metastasis is the reason for suggesting that these nodules are cancers.

Thyroid nodules of this type, usually labeled cancers by the investigators who have studied them, have been induced in rats or mice by several experimental maneuvers which lead to excessive thyrotropic stimulation: iodine-deficient diet, partial destruction of the thyroid by radioiodine, feeding with one or another antithyroid drug, and even partial thyroidectomy. These experiments clearly show that there is no unique carcinogenic action of any one antithyroid compound. It is important, too, that no known antithyroid compound has ever been implicated in the induction of cancers elsewhere in the body, even when fed to rats or mice in large doses for a long time (Morris: *Advances in Cancer Res.* 3:51, 1955, and Isler: *J. Nat. Cancer Inst.* 23:675 [Oct.] 1959).

In order to be designated as carcinoma, thyroid nodules would have to grow autonomously, but no one has yet succeeded in producing such a nodule. When the goitrogenic influence of excessive thyrotropic stimulation is relieved, the nodules regress. This result may be achieved by removing the antithyroid compound from the diet, by giving iodine to iodine-deficient animals, or by giving thyroid hormone in any of the experimental designs. One exception to this generalization is a most interesting type of benign nodule, designated as type γ and described by Isler and Leblond, which apparently is accelerated in growth when iodine is given to animals raised on a diet low in iodine. Autonomous carcinoma of the thyroid has been induced only by serial transplantation of thyroid tissue through several generations of thyroid-deficient animals. The animal experiments forming the basis of the conclusion that aminotriazole causes carcinoma of the thyroid have not been published and are not accessible for evaluation. Apparently they were not extensive and thyroid deficiency was not taken into account and corrected by supplement of thyroid hormone. No antithyroid drug yet studied leads to thyroid enlargement or nodular goiter when thyroid deficiency is prevented.

Several antithyroid drugs, thiouracil, mercaptoimidazole, and derivatives thereof, have been widely used in the treatment of hyperthyroidism in the past 17 years, and no instance of the induction of carcinoma has been encountered. The doses used for this purpose were much larger than the quantity of aminotriazole that would derive from the most highly contaminated cranberries. Still larger doses would be needed in man to reproduce thyroid changes comparable to those induced in rats, and presumably dosage would have to be continued for most of a lifetime. Meanwhile, a progressively enlarging goiter would make its appearance, the subject would lapse into profound myxedema, and the execution of the experiment would be intolerable. It seems inconceivable, therefore, that an antithyroid compound, no matter how potent and however prevalent in food, could ever lead to the development of the sort of thyroid nodules elicited in rats.

In 1949 it was shown that the edible portions of certain vegetables of the mustard family, notably the rutabaga or yellow turnip and the seeds of many others, yielded on extraction L-5-vinyl-2-thiooxazolidone, an antithyroid compound accounting for the goitrogenicity of these foods (Astwood; Greer; and Ettlinger: *J. Biol. Chem.* 181:121 [Nov.] 1949). A rough estimate, based on insufficient data, would suggest that these Swedish turnips may be 100 times as potent as cranberries "badly contaminated" with aminotriazole. The reason for studying these foodstuffs was to determine whether they played a part in the mysterious prevalence of goiter in regions where iodine deficiency was not a cause. In spite of continuing inquiry for several years, I have not been able to trace a single instance of even simple goiter to the excessive ingestion of vegetables such as the rutabaga. It is also of interest that among the first means of inducing the growth of nodules in the thyroids of rats was the feeding of a diet made up of corn meal and rolled oats supplemented with calcium chloride (Hellwig: *Am. J. Cancer* 23:550 [March] 1935) and a mixed diet containing rape seed, which was more effective (Griesbach; Kennedy; and Purves: *Brit. J. Exper. Path.* 26:18 [Feb.] 1945). The lesion has since been induced by the incorporation in the diet of thiourea, thiouracil, methylthiouracil, propylthiouracil, and now aminotriazole.

Before the cranberry episode my associates and I had been looking for an antithyroid compound that might have a longer duration of action than those currently in use for the treatment of hyperthyroidism and Dr. W. E. Mayberry had found that aminotriazole might be such a compound. A single oral dose of 100 mg. inhibited radioiodine uptake by the thyroid of normal and thyrotoxic subjects for 24 hours, which means that there is a possibility of therapy with one dose per day; 10 mg. had only a slight effect. Should experience show the compound to be well tolerated, we will be faced with the anomalous situation that an effective remedy suitable for human use is banned from use in killing weeds.

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Boston 15.

DEATH FROM USE OF THROAT LOZENGE

To the Editor:—The conclusions in the article, "Anaphylactic Death from Use of Throat Lozenge," by Hesch in The Journal, Jan. 2, page 12, are subject to question. Sudden laryngeal obstructi in the presence of sore throat and hoarseness wi out evidence of previous respiratory difficulty is well-known clinical entity. The edema is usua located in the epiglottis. I have seen two patie who had sore throats but who were not hoarse a were not given medicaments develop sudden c struction requiring emergency tracheotomy. In o of these, the patient was in the operating roo awaiting orderly tracheotomy because the ede was diagnosed when sudden obstruction occurr

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Michael B. Shimkin, M.D.
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IDEALS IN MEDICINE

To the Editor:—Who among us cannot recall wi longing the idealisms of our student and inte days or taste with remorse the disillusionment these ideals? Is not the most bitter disillusionme of all that of strife within our own professio Physicians, being human, share with other peop the frailties of sin and failure. They also sha the common desire for acceptance, recognition, an praise. Similarly, they react to oppression, crit cism, and threats to freedom with suspicion an hate. To whom can we turn for solace and su port when we fail, if not to one another.

The fundamental purpose of the physician ha always been and shall ever be to heal the min and body of his fellow man. It would seem incor gruous that, with so powerful an adversary a death, we find energies to devote to petty bickering and puerile lust for political power. Expending energy jockeying for position is neither mature nor intelligent and causes a terrible loss of scientific productivity. Ideals which have motivated most young physicians are being weakened by sarcasms and adverse witticisms. Common codes of courtesy are being destroyed by gossip and defamation.

Are we so insecure we cannot praise our fellow physician, whether he be general practitioner or specialist? Can we not simply refrain from saying anything about him if we cannot say something good? Do we not understand that by innuendoes and faint praise we destroy ourselves? Do we increase our stature by ridiculing the advances of others? Can we not recognize that if we simply ignore those out of step in our midst they must conform or perish? Is it not time that we leave battles to the warriors and politics to the politicians and return to the pursuit of our science and the care of the sick? Our work is the best in life and our ideals should be the finest. We have nothing of which to be ashamed. Let us join hands and daily reaffirm these ideals to ourselves, profess them to all who will listen, and strive ever to live by them.

Banning G. Lary, M.D.
1550 N.W. 10th Ave.
Miami 36.

FOREIGN MEDICAL GRADUATES

To the Editor:—The editorial, entitled "America's Responsibility to the Foreign Medical Graduate," which appeared in The Journal, Nov. 14, 1959, page 1577, deserves wide reading and the approbation of all American physicians and others who are involved in the problems of meeting America's health needs. Since World War II, foreign medical graduates have been an important factor in reducing the gap between the physician population and the general population in the United States. They have also filled many thousands of internships and residencies in the hospitals in this country which would otherwise have been vacant. The National Committee for Resettlement of Foreign Physicians, since its founding in 1939, has provided evaluation and placement services for foreign physicians. These services have been provided primarily for escapees and voluntary immigrants, but help has also been given to a limited number of exchange students. The committee has worked to maintain the high standards of medical practice of the United States, and service has not been given to candidates whose training was considered substandard.

It is with pleasure, therefore, that we read this editorial which places the responsibility for initiating continuing programs that will insure proper educational opportunities for the foreign medical graduate on hospital staffs, administrators, and specialty certifying boards. It is to the interest of all, but especially of the sick in hospitals, to be attended by skillful and well-trained interns and resident physicians. The chaotic, uncontrolled situation of the last decade, in which thousands of unscreened foreign physicians, with untested language facility and unknown professional skills, were accepted for house staff positions, often sight unseen, has been tragic for all concerned. The Educational Council for Foreign Medical Graduates has been helping to solve this problem by screening these persons overseas, but the voluntary immigrant who arrives legally, under federal immigration laws, must be tested and advised in this country for hospital placement and for postgraduate education.

Our committee, with an annual intake of several hundred new foreign medical graduates each year, can provide placement services for only a fraction of the 9,000 to 10,000 foreign physicians in training in the United States. We believe it is now time for one of the national medical agencies with greater resources and staff than ours to face the problems presented by the continuing wave of medical immigrants and exchange students. It is the only way that an orderly guidance and placement program can be provided for all foreign physicians in the United States.

Robert Boggs, M.D., Chairman
Alex M. Burgess, M.D.
Irving Graef, M.D., Vice-chairmen,
National Committee for Resettlement of
Foreign Physicians, Inc.
31 Union Square West
New York 3.

To the Editor:—The editors should be congratulated for suggesting, in the editorial appearing in The Journal, Nov. 14, "America's Responsibility to the Foreign Medical Graduate," a common agreement with regard to the basic eligibility of the fully qualified foreign physician for certification by American specialty boards. Being a graduate physician from India, I am personally concerned, and although it is just a suggestion it will be warmly received by foreign doctors generally.

The banning of foreign graduates from American specialty board examinations has always been the greatest single hindrance to the physicians of my own country in pursuing postgraduate experience and gaining prestige in the United States, mecca of world medicine. Foreign physicians have struggled be intolerable. It seems inconceivable, therefore, that an antithyroid compound, no matter how potent and however prevalent in food, could ever lead to the development of the sort of thyroid nodules elicited in rats.

In 1949 it was shown that the edible portions of certain vegetables of the mustard family, notably the rutabaga or yellow turnip and the seeds of many others, yielded on extraction L-5-vinyl-2-thiooxazolidone, an antithyroid compound accounting for the goitrogenicity of these foods (Astwood; Greer; and Ettlinger: *J. Biol. Chem.* 181:121 [Nov.] 1949). A rough estimate, based on insufficient data, would suggest that these Swedish turnips may be 100 times as potent as cranberries "badly contaminated" with aminotriazole. The reason for studying these foodstuffs was to determine whether they played a part in the mysterious prevalence of goiter in regions where iodine deficiency was not a cause. In spite of continuing inquiry for several years, I have not been able to trace a single instance of even simple goiter to the excessive ingestion of vegetables such as the rutabaga. It is also of interest that among the first means of inducing the growth of nodules in the thyroids of rats was the feeding of a diet made up of corn meal and rolled oats supplemented with calcium chloride (Hellwig: *Am. J. Cancer* 23:550 [March] 1935) and a mixed diet containing rape seed, which was more effective (Griesbach; Kennedy; and Purves: *Brit. J. Exper. Path.* 26:18 [Feb.] 1945). The lesion has since been induced by the incorporation in the diet of thiourea, thiouracil, methylthiouracil, propylthiouracil, and now aminotriazole.

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The fundamental purpose of the physician has always been and shall ever be to heal the mind and body of his fellow man. It would seem incongruous that, with so powerful an adversary as downtown Los Angeles. 3. There are no "halo" patterns over freeways and automobile raceways. 4. Aerial views show smog originating at industrial sources. 5. If the automobile contribution were as important as supposed, why would smog not form over large accumulations of cars, such as at the Rose Bowl parade and at Santa Anita race track? 6. Why does smog always originate in the same industrial refinery areas?

If it were due to cars, would it not originate at least once in Santa Monica, Burbank, or Beverly Hills?

Martin J. Rosten, M.D.
596 Westwind Drive
El Cajon, Calif.

IRRADIATED BLOOD-TYPING SERUM

To the Editor:—In the first paragraph of a paper entitled "Irradiated Blood-Typing Serum" by Robert M. Jamison in The Journal, Jan. 23, page 334, it was stated that "a search of the literature does not reveal any previous studies of this problem." Dr. David Macht and others have written papers on the reactions of serums which have been radiated with roentgen rays (*Am. J. Roentgenol.* 61:534-542 [April] 1949). While these papers did not deal with blood typing of serums per se, they dealt with the changes which occur in serum when it is irradiated.

Stanley H. Macht, M.D.
Washington County Hospital
King and Antietam streets
Hagerstown, Md.

USE OF NEOMYCIN IN RETROGRADE PYELOGRAPHY

To the Editor:—In The Journal, page 236, there is a clinical note by Hoffman and Carvalho entitled "Retrograde Pyelography and Use of Contrast Mediums Containing Neomycin." There can be no quarrel with the authors' observations in two parallel series of 100 patients each with retrograde pyelography with and without the addition of 2.5% neomycin as an antimicrobial additive. In each series two patients with bacteremic episodes were observed. These required supplementary antibiotic therapy.

We take issue, however, with the authors' conclusion that "the prophylactic or therapeutic value of the addition of neomycin sulfate to opaque mediums seems insufficient to justify its use at an increased cost." Let us consider the added cost. Agreeing wholeheartedly with the authors that 3 cc. of contrast medium is adequate for visualization of the usual renal pelvis, and allowing for bilateral pyelograms in every case, plus the loading of a syringe with 5 cc. of contrast medium for good measure, we conclude that a 5-Gm. ampul. of neomycin sulfate, which costs a hospital well under $10, will serve 20 patients at an added cost of about 50 cents per patient. Cystoscopy with retrograde pyelography is a sufficiently expensive procedure so that the 50-cent addition is scarcely a major consideration.

More important is the suspicion that the authors have overlooked the virtue of the additive that they used, which is surely not for the purpose of permitting overdistension of the pelvis or of covering up any damage resulting from improper technique. In the years previous to our use of an additive we collectively have seen about four patients with fulminating parenchymal renal infections that seemed possibly to be due to the retrograde introduction of pathogens. A few other patients have been seen in whom a previously uninfected hydronephrotic kidney or a kidney containing calculi presumably became first infected after retrograde procedures. Such a condition, leading to a nephrectomy that would otherwise not have been deemed necessary, kindled our enthusiasm for a study of additives six years ago. Up to the present, several thousand pyelograms later, we have found no cause to regret the use of neomycin and we have, which is more important, felt that the applicability of retrograde pyelography has been extended.

Prior to use of neomycin we were reluctant to use retrograde injection techniques to study a kidney which did not excrete the contrast medium given intravenously if this required an approach through an infected bladder. This is still not done with gay abandon or as a matter of routine, but it has now been done many times without mishap. Hoffman and Carvalho provided no information in respect to presence or absence of infection in their patients, and no special significance can be attached to a series of retrograde pyelograms with reactions in 2% of patients since a complete absence of significant reactions in 100 patients might be accepted with equanimity. Perhaps, if the present Senate investigation persists, the cost of the additive may become even less of a consideration, in which case to ignore the added protection of neomycin in retrograde mediums will be even more penny-wise than it seems now to be. May we respectfully commend its use to all who undertake retrograde pyelography.

Russell B. Roth, M.D.
Elmer Hess, M.D.
Anthony F. Kaminsky, M.D.
Harold J. McLaren Jr. M.D.
501 Commerce Bldg.
Erie, Pa.

to climb the ever narrowing pyramid of residency training for five or six golden years of their lives in the United States, only to find at the end that they are discriminated against. They return home discouraged, disgusted, and without any concrete evidence of their proficiency. This is indeed a sad and traumatic experience. As a result, at least 90% of Indian doctors who plan to further their studies abroad are only too glad to proceed to England where they are accepted with open arms and fair treatment. A small percentage of the rest, to which I belong, prefer to obtain the teaching on this side of the Atlantic, in spite of the obstacles, and come to Canada instead so that they may be exposed to whatever American influences may have permeated here.

It is understandable, and desirable, that the American specialty boards maintain a high professional standard, but banning a foreign doctor, who comes from a fully approved medical school in his own country and has completed the required course of approved graduate residency training on American soil, from the examinations is a bitter instance of discrimination. Foreign students of today will be their countries' mainstay tomorrow. They could return home pro-American, bringing the American culture and way of life. No one can deny that, in these days of international conflict, mutual understanding and cooperation among various peoples of the world *is the only means* for the promotion of world peace.

May I venture to say that if the United States, the mecca of medicine, is to compete successfully with the United Kingdom, Canada, Germany, and even Russia, all of which allow foreign graduates to take their specialty board examinations, it is time that an effort be made to facilitate rather than to hinder the pursuit of undergraduate and graduate training of students from foreign lands.

HENRY S. GUPTA
Montreal, Quebec.

SMOG IN LOS ANGELES

To the Editor:—The article on smog by Motley and co-workers in THE JOURNAL, Nov. 14, 1959, page 1469, contains a common misstatement which should be corrected. The major source of smog in Los Angeles is industry, not automobiles as stated. Proof of this statement follows. I might add that the automobile is used as a convenient red herring to shield industry.

The figures are in tons per day. Automobile figures include trucks and buses. In the San Francisco bay area figures are from the Air Pollution Control District; Jan. 16, 1959. These figures are more reliable than those for Los Angeles, since the county is more compact.

Even though these figures show automobile to constitute less than half of the contributions they are completely unreliable for the followin reasons: 1. Automobile statistics are based on gasoline consumption for the entire county. Obviousl many automobiles are in nonsmoggy areas. The Ai Pollution Control District estimates that th automobile's contribution for the center of th county is only one-fifth of the total. 2. While automobile gas consumption remains fairly constant fiv days a week, on Saturday and Sunday the smo pattern should be markedly different. This is not s Even on these days smog clouds originate from th same industrial refinery area. 3. The figures fo industry are inaccurate for several reasons: (a while a chimney is being monitored the owners ca control its emanations; (b) the figures are based o a yearly average, but industrial contaminatio comes in peaks. For instance, power plants burn o only when gas is not available. This is brought o by the Air Pollution Control District news release of April 30, 1959, in which it was stated tha enforcement of rule 62 would prevent as much a 800 tons of sulfur dioxide on a day of peak use. Th figure previously given for total sulfur from a sources was only 550 tons per day; (c) proof i available that refineries contaminate the air primarily at night (one observer took photograph around the clock to demonstrate this).

Component Parts of Smog

	Petro-chemical Industry	Combustion and Fuel Oil	Metal-lurgical Industry	Automotiv
Hydrocarbons	572	1	17	579
Sulfur	234	177	104	30
Nitrogen oxides ..	55	86	00	237
Total	861	264	121	846
Grand total ..	1,246 vs. 846			

The figures for the Los Angeles area are as follows:

	Industry and Fuel Combustion	Petroleum Refining, Storing, and Marketing	Automotive
Hydrocarbons	186[*]	250[*]	550-1,100[§]
Sulfur oxides	400[*]	150[‡]	34-48[§]
Nitrogen oxides	260[†]	56[‡]	137-412[§]
Organic gases	176[*]	2[*]	27[*]
Total of averages	1,022	458	1,119
Grand total	1,480 vs. 1,119		

Circumstantial evidence includes the followin facts: 1. Smog originated in 1942, during gasolin rationing but concurrently with the introductio of a new cracking process at the refineries. 2. Vernon, an industrial district, has more smog alerts tha downtown Los Angeles. 3. There are no "halo" patterns over freeways and automobile raceways. 4. Aerial views show smog originating at industrial sources. 5. If the automobile contribution were as important as supposed, why would smog not form over large accumulations of cars, such as at the Rose Bowl parade and at Santa Anita race track? 6. Why does smog always originate in the same industrial refinery areas?

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[*] Chambers, L. A.: Air Pollution: Where Does It Come from? re before the National Conference on Air Pollution, Los Angeles, Nove ber, 1958.

[†] Chase, R.: Extent to Which Control Techniques Have Been Utiliz in Los Angeles County, read before the National Conference on A Pollution, Los Angeles, November, 1958.

[‡] Griswold, S.: Sources of Air Pollution in Refineries, read before t National Conference on Air Pollution, Los Angeles, November, 19

[§] Chambers, L. A.: Automotive Vehicles as Air Pollution Source read before the National Conference on Air Pollution, Los Angel November, 1958.

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Stanley H. Macht, M.D.
Washington County Hospital
King and Antietam streets
Hagerstown, Md.

USE OF NEOMYCIN IN RETROGRADE PYELOGRAPHY

To the Editor:—In The Journal, page 236, there is a clinical note by Hoffman and Carvalho entitled "Retrograde Pyelography and Use of Contrast Mediums Containing Neomycin." There can be no quarrel with the authors' observations in two parallel series of 100 patients each with retrograde pyelography with and without the addition of 2.5% neomycin as an antimicrobial additive. In each series two patients with bacteremic episodes were observed. These required supplementary antibiotic therapy.

We take issue, however, with the authors' conclusion that "the prophylactic or therapeutic value of the addition of neomycin sulfate to opaque mediums seems insufficient to justify its use at an increased cost." Let us consider the added cost. Agreeing wholeheartedly with the authors that 3 cc. of contrast medium is adequate for visualization of the usual renal pelvis, and allowing for bilateral pyelograms in every case, plus the loading of a syringe with 5 cc. of contrast medium for good measure, we conclude that a 5-Gm. ampul. of neomycin sulfate, which costs a hospital well under $10, will serve 20 patients at an added cost of about 50 cents per patient. Cystoscopy with retrograde pyelography is a sufficiently expensive procedure so that the 50-cent addition is scarcely a major consideration.

More important is the suspicion that the authors have overlooked the virtue of the additive that they used, which is surely not for the purpose of permitting overdistension of the pelvis or of covering up any damage resulting from improper technique. In the years previous to our use of an additive we collectively have seen about four patients with fulminating parenchymal renal infections that seemed possibly to be due to the retrograde introduction of pathogens. A few other patients have been seen in whom a previously uninfected hydronephrotic kidney or a kidney containing calculi presumably became first infected after retrograde procedures. Such a condition, leading to a nephrectomy that would otherwise not have been deemed necessary, kindled our enthusiasm for a study of additives six years ago. Up to the present, several thousand pyelograms later, we have found no cause to regret the use of neomycin and we have, which is more important, felt that the applicability of retrograde pyelography has been extended.

Prior to use of neomycin we were reluctant to use retrograde injection techniques to study a kidney which did not excrete the contrast medium given intravenously if this required an approach through an infected bladder. This is still not done with gay abandon or as a matter of routine, but it has now been done many times without mishap. Hoffman and Carvalho provided no information in respect to presence or absence of infection in their patients, and no special significance can be attached to a series of retrograde pyelograms with reactions in 2% of patients since a complete absence of significant reactions in 100 patients might be accepted with equanimity. Perhaps, if the present Senate investigation persists, the cost of the additive may become even less of a consideration, in which case to ignore the added protection of neomycin in retrograde mediums will be even more penny-wise than it seems now to be. May we respectfully commend its use to all who undertake retrograde pyelography.

Russell B. Roth, M.D.
Elmer Hess, M.D.
Anthony F. Kaminsky, M.D.
Harold J. McLaren Jr. M.D.
501 Commerce Bldg.
Erie, Pa.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Metalloenzymes and Myocardial Infarction: III. Lactic Dehydrogenase Activity of Serum—A Determinate Diagnostic Measure. P. J. Snodgrass, W. E. C. Wacker, E. C. Eppinger and B. L. Vallee. New England J. Med. 261:1259-1266 (Dec. 17) 1959 [Boston].

Interest in the diagnostic value of the metalloenzymes in myocardial infarction began when a marked increase in serum copper value after in*farction was observed in 1952. Later the serum* concentration of another metal, zinc, was investigated. Since zinc is a component of lactic acid dehydrogenase (LDH), the activity of this enzyme was studied in the serum of patients with acute myocardial infarction, and a marked increase in activity was found. Assay of the serum LDH proved to be a simple, precise, and accurate method for the diagnosis of acute myocardial infarction. The authors investigated the serum LDH activity in 1,250 tests on 500 patients hospitalized in the Peter Bent Brigham Hospital, Boston. There was no selection of cases other than that conditioned by the judgment of the physicians in charge, who requested determinations whenever the information was deemed potentially useful in differential diagnosis. In 308 of the 500 patients the measurements were requested primarily as diagnostic aids in various cardiovascular diseases. The remaining 192 cases represented a wide spectrum of other medical diseases seen at a general hospital.

All LDH measurements were performed with a Beckman DU spectrophotometer at 23 C and later with a simple, portable, monochromatic, ultraviolet photometer. In every patient in whom acute myocardial infarction was proved, and in whom measurements were made between the 2nd and the 10th day after onset, the serum LDH activity was elevated significantly. False-negative results did not occur in any of the 28 cases proved by autopsy or in 66 patients with electrocardiograms considered diagnostic by established, classic criteria. Moreover, 4 patients with LDH activity in the normal range, who were thought to have sustained an acute myocardial infarction by other criteria, were proved at autopsy not to have the disease. An elevated serum LDH activity is, therefore, a necessary confirmatory criterion for the diagnosis of acute myocardial infarction. The addition of this method to those currently employed in the diagnosis of acute myocardial infarction should permit the diagnostic accuracy to approach 100%. The *existence of increased LDH activity always denotes* serious disease, and should lead to further diagnostic search for the underlying cause.

Glycogen Liver in Diabetes Mellitus: An Iatrogenic Acute Abdominal Condition. A. Schotte, H. K. Lankamp and M. Frenkel. Nederl. tijdschr. geneesk. 103:2258-2262 (Nov. 7) 1959 (In Dutch) [Amsterdam].

The authors present the history of a 40-year-old woman who had diabetes mellitus that was difficult to control. She had been receiving antidiabetic treatment for 7 years, and at the time she was hospitalized, in a precomatose condition, she had been maintained on dietetic treatment and on 40 units of a delayed-action insulin daily. Two days previously she had awakened with an abdominal pain, so severe that morphine had to be administered. The following day she began to vomit and reduced her insulin dose to 10 units. She was brought to the hospital when she became increasingly comatose. Examination revealed hyperglycemia and diabetic acidosis, with sugar, acetone, and diacetic acid in the urine. With the administration of 180 units of insulin (in the first 24 hours) and of isotonic sodium chloride solution, the diabetic *acidosis improved rapidly*, but the appetite remained poor and the abdominal pain persisted. Subsequently, the patient had several recurrences of the attacks of abdominal symptoms, and painful hepatomegaly became increasingly evident. When among other diagnoses a rapidly growing metastasis from a sarcoma was suspected, laparotomy was performed. It was found that the liver contained excessive deposits of glycogen and some fat, and these changes were believed to be the cause of the symptoms.

The patient was freed from her attacks when she was given an additional dose of insulin at midnight. It is believed that the attacks were probably of iatrogenic origin, in that they were probably

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The place of publication of the periodical appears in brackets preceding each abstract.

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brought on by an overdosage of invert sugar and of insulin, resulting in a temporary exhaustion of the glycogenolytic enzyme system of the liver. Injection of either epinephrine or glucagon during the recovery phase did not reveal any permanent abnormality of the glycogenolytic system. Knowledge of this syndrome will prevent unnecessary laparotomy.

Long-Term Results in Corrected Fibrillation. P. Broustet, H. Bricaud, P. H. Blanchot and J. C. Chignon. Semaine hôp. Paris 35:3085-3089 (Nov. 18) 1959 (In French) [Paris].

The authors report the long-term results in 186 patients in whom conversion of chronic atrial fibrillation was obtained with quinidine treatment. The duration of fibrillation prior to treatment varied from several weeks to several months. It was possible to sustain normal sinus rhythm in 163 of the patients for periods ranging from 3 months to 6 years with small maintenance doses of quinidine, regardless of the origin of fibrillation. There was an evident clinical improvement in all these patients. The degree of improvement was more marked in patients with less severe cardiac involvement. In 41 of the 186 patients the discontinuation of quinidine treatment after restoration of normal sinus rhythm was followed by a recurrence of fibrillation, which was associated, particularly in those with mitral stenosis, with exacerbation of cardiac insufficiency or with the appearance—or reappearance—of arterial embolism. Normal sinus rhythm was again restored in some of these patients with the reinstatement of larger doses of quinidine. The comparison between 2 identical groups of patients with atrial fibrillation, one of which was given quinidine treatment, while in the other this therapy had not been tried or had not been successful, showed that the probability of survival and of the return to normal function was far better in the treated group.

Studies in Man on Hyper- and Hypoaldosteronism. S. R. Hill Jr., J. F. Nickerson, S. B. Chenault and others. A. M. A. Arch. Int. Med. 104:982-994 (Dec.) 1959 [Chicago].

The authors determined the aldosterone, 17-ketosteroid, and 17-hydroxycorticosteroid levels in the urine and the sodium and potassium levels in the serum and urine during control periods, during periods of inhibition of adrenal cortical secretory activity by Amphenone B [3,3-bis (*p*-aminophenyl)-2-butanone], and during periods of stimulation by sodium withdrawal and potassium administration in 5 patients with secondary hyperaldosteronism, 1 patient with primary hyperaldosteronism, and 1 patient with primary hypoaldosteronism. Similar studies were made in normal persons for comparison. Of the 5 patients with secondary hyperaldosteronism, this condition resulted from intercapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome) in 1, from congestive heart failure in 2, and from cirrhosis of the liver in 2. The results of the studies in these 5 patients showed that Amphenone (1 Gm. dissolved in 1,000 cc. of 5% dextrose in water) may be administered intravenously for at least 23 days without toxic effects, except when severe disease of the liver is present. In the patient with the Kimmelstiel-Wilson syndrome, Amphenone, administered in this manner, induced a twofold increase in sodium excretion, a marked water diuresis, and a clinical remission beginning 10 days after the institution of the therapy. Glucocorticoid suppression also began about 5 days after the administration of Amphenone was started. In the 2 patients with congestive heart failure, sodium and water diuresis failed to occur even though elevated urinary aldosterone levels were reduced to normal by the administration of Amphenone. This implies that other abnormalities, presumably hemodynamic, are more important than elevated aldosterone levels in causing and maintaining edema in these patients with congestive heart failure.

The patient with primary hyperaldosteronism, a 54-year-old man, was completely asymptomatic except for severe hypertension of 12 years' duration; the hypertension was completely ameliorated by the subtotal removal of the bilaterally hyperplastic adrenals, which emphasizes the necessity of correct diagnosis and definite surgery. A decreased serum potassium level assumes major diagnostic importance in patients with hyperaldosteronism, as symptoms suggesting hypopotassemia may be absent, and urinary aldosterone levels may either not be consistently elevated or be elevated secondarily. The use of antihypertensive drugs which cause potassium diuresis and consequent hypopotassemia makes this diagnostic index also open to question. However, in most patients treated with these compounds, the serum sodium concentration is low, rather than normal or high as seen in patients with hyperaldosteronism. If, at the time of adrenal exploration, an adrenal adenoma is found, the surgeon's course of action is clear. If, however, the adrenals appear normal, the diagnosis should have been well enough established beforehand to be able to advise subtotal adrenalectomy despite this. Repeated determination of serum sodium and potassium levels still remains the most satisfactory method now readily available for making such a diagnosis.

The patient with primary hypoaldosteronism, a 62-year-old man, showed abnormalities in potassium metabolism in addition to relative primary deficiency of aldosterone. Patients with total bilateral adrenalectomy, who are being maintained on glucocorticoids alone, do not always manifest abnormalities in potassium metabolism. It is possible, however, that the follow-up has not been long enough or that the dietary conditions have not been provocative enough for these patients to show this syndrome. The production of a hypothetical antialdosterone substance could theoretically produce electrolyte abnormalities identical to those reported This patient could not tolerate either severe sodium restriction or potassium loading, unless desoxycorticosterone was simultaneously administered. His condition, however, was fairly well maintained on a moderately high sodium and moderately low potassium intake, without added steroids. The urinary 17-hydroxycorticosteroid excretion of the patient did not increase on prolonged sodium restriction. The question as to how much of the patients' clinical picture of shortness of breath and musculoskeletal pains can be attributed to the inadequate aldosterone response and how much to renal disease cannot be completely answered, although the results of the studies favor the former as the dominant cause of the findings.

Diabetic Nephropathy: A Clinical and Pathologic Study Based on Renal Biopsies. D. D. Gellman, C. L. Pirani, J. F. Soothill and others. Medicine 38:321-367 (Dec.) 1959 [Baltimore].

In 1936 Kimmelstiel and Wilson described peculiar hyaline masses in the centers of the glomerular lobules in 8 elderly patients, 7 of whom had diabetes. They called the process "intercapillary glomerulosclerosis," but since their illustrations emphasized the circular cross sections of the masses, the term "nodular" was used by some investigators to distinguish the lesion from other varieties of glomerulosclerosis. In addition to the nodular lesion, the term "intercapillary glomerulosclerosis" has been applied to a diffuse process which frequently involves the glomerulus in diabetics, for the so-called exudative lesion, and even for a clinical syndrome.

Three main points have been at issue: (1) whether the lesion is specific for diabetes; (2) whether it is really the cause of the clinical syndrome which Kimmelstiel and Wilson found in their patients; and (3) whether the lesion is intercapillary or not. The authors describe clinical and pathological studies on 53 patients with diabetes mellitus. Each patient had at least one renal biopsy; some had more than one. At the time of each biopsy clinical and laboratory investigations were made, and the results correlated with the severity of the histological lesions. Nine patients subsequently came to autopsy. All the histological features which have been described in the kidney in diabetes mellitus were seen in this series.

Diffuse diabetic glomerulosclerosis was present in 75% of the biopsies and all the autopsies. The lesion consisted of a uniform deposition of abnormal hyaline material, rich in mucopolysaccharides, in and around the capillary walls, with early narrowing and eventual obliteration of the capillary lumens. Nodular diabetic glomerulosclerosis was the glomerular lesion next in frequency to diffuse diabetic glomerulosclerosis. It was found in 48% of the biopsies and in 8 of the 9 autopsies. Nodular glomerulosclerosis of the diabetic type was not found in more than 600 renal biopsies in nondiabetic patients.

Nodular diabetic glomerulosclerosis was always accompanied by diffuse diabetic glomerulosclerosis, but the diffuse lesion sometimes occurred alone. When the severity of nodular diabetic glomerulosclerosis was plotted against the height of the diastolic blood pressure, the amount of proteinuria, the levels of serum urea nitrogen, serum creatinine, and serum albumin, or the urea or creatinine clearance, a constant pattern of relationship was found. The presence of nodular glomerulosclerosis was associated with abnormal findings in each test, but there was no tendency for the test to become increasingly abnormal as nodular glomerulosclerosis becomes more severe. Similarly the presence of nodular glomerulosclerosis was associated with an increased incidence of episodes of ketosis, of diabetic retinopathy, and of edema and the nephrotic syndrome, but the incidence did not increase further with increasing severity of nodular glomerulosclerosis.

By contrast, increasing severity of diffuse diabetic glomerulosclerosis was closely correlated with increasing diastolic blood pressure, proteinuria, and serum urea nitrogen and creatinine levels; with decreasing serum albumin levels and urea and creatinine clearances; and with increasing incidences of ketosis, retinopathy, edema, and the nephrotic syndrome. It was suggested that the abnormalities associated with the presence of nodular glomerulosclerosis are, in fact, caused by the diffuse glomerulosclerosis which invariably accompanies the nodular lesion. It was concluded that nodular glomerulosclerosis, the "Kimmelstiel-Wilson lesion," though of great diagnostic value, is of little functional importance. The nephrotic syndrome combined with renal failure in diabetes is not caused by this lesion and, therefore, should not be called the Kimmelstiel-Wilson syndrome. These changes in renal function are caused by diffuse diabetic glomerulosclerosis and by the associated arteriolar and tubular lesions.

Parathion Intoxication with Complicating Cardiac Arrhythmia: Three Cases. T. O. Iversen. Ugesk. læger 121:1735-1736 (Nov. 5) 1959 (In Danish) [Copenhagen].

In 2 of the 3 cases reported of Parathion intoxication combined with cardiac arrhythmia, the atrial fibrillation disappeared with other symptoms of the poisoning. In the third case, however, the premature ventricular contractions and variations persisted after other symptoms of acute intoxication had disappeared, but the cardiogram became normal after digitalization. Intoxication with Parathion depends on the ability of the substance to inhibit the activity of the organism's cholinesterases. The arrhythmia is ascribed to the action of acetylcholine.

Acute Intermittent Porphyria: A Family Study. D. H. Cannow, E. H. Morgan and G. A. Sarfaty. Australasian Ann. Med. 8:267-271 (Nov.) 1959 [Sydney, Australia].

The incidence of acute or latent porphyria was studied in several interrelated family groups after the death from acute intermittent porphyria of a 27-year-old woman. Each family group was personally visited, and a medical history of each member was obtained. Evening and morning urine specimens were collected and tested for porphobilinogen. Stool specimens were obtained from 36 members of the total family. Both urine and feces were stored at −20 C. and quantitative estimations were made within 2 to 4 days by the Watson and Schwartz technique. The results were interpreted according to 3 categories, namely, acute porphyria (presence of clinical and chemical stigmata), latent porphyria (excretion of abnormal quantities of porphobilinogen and porphyrins without clinical symptoms), and normal (absence of clinical symptoms and of urinary or fecal excretion).

Acute porphyria was diagnosed in 5 members of the total family, and latent porphyria was diagnosed in 6, including the father of the original patient whose death gave way to this investigation. The incidence of porphyria in this family is compatible with inheritance by a non-sex-linked dominant gene (5 of the porphyric members were male and 6 were female). The porphyric disorder was found in 3 successive generations, with transmission from father to daughter and from mother to son. The highest incidence was in the third generation, in which 9 out of 16 members had either acute or latent porphyria. The findings in this study are clinically, genetically, and biochemically identical with those of Waldenström's familial studies in Sweden.

Occurrence of Miliary Tuberculosis as Malignant Neoplastic Disease. B. Zachau-Christiansen. Ugesk. læger 121:1721-1728 (Nov. 5) 1959 (In Danish) [Copenhagen].

The author discusses the difficulty in diagnosis of acute generalized tuberculosis, especially in older persons, in whom the clinical picture can suggest a hopeless case of cancer. French authors speak of a "forme pseudoneoplasique." The differential diagnosis between malignant neoplastic diseases and malignant tuberculous diseases will always be so difficult that all diagnostic and therapeutic attempts must be made. In uncertain cases the final diagnosis should be established by biopsy or operation. In the first of the 3 cases described, the diagnosis was based on pathologicoanatomic examination and cultivation of tubercle bacilli; in the second case, on the histological picture; and in the third case, on the microscopic cellular picture. The cases reported to date indicate that, if there is to be hope of helping this category of patients, modern antituberculous agents must be applied on clinical suspicion alone. Therapy of miliary tuberculosis should consist in treatment with PAS, streptomycin, and isoniazid in largest possible doses. Continued treatment for at least 9 months is recommended; Lesorbe and Oury advise up to 3 years.

Occlusion of the Hepatic Veins in Man. R. G. F. Parker. Medicine 38:369-402 (Dec.) 1959 [Baltimore].

Occlusion of the hepatic veins (Chiari's or Budd-Chiari's syndrome) is comparatively rare, and the literature on this condition consists mostly of individual case reports. In studies at the Bernhard Baron Institute of the London Hospital, the author was able to study a large number of cases, including 149 previously reported, in which there was evidence of hepatic vein occlusion during life and in which the diagnosis was confirmed at autopsy, as well as 15 others from the London Hospital. Hepatic vein occlusion occurs with approximately equal frequency in either sex. It may occur at any age, but is especially common in the third and fourth decades. The duration of symptoms has varied from 2 days to 23 years. In only 20% of the patients did the illness last less than 1 month; in 55% it lasted 3 months or longer, and in 25% a year or more. In cases of short duration there were often vague prodromal symptoms, and the vascular lesions were often more chronic than was anticipated from the clinical history.

Hepatic vein occlusion may present in one of 5 ways: (1) in about 76% of cases as a subacute or chronic illness dominated by severe ascites; (2) as an acute illness with more or less evidence of hepatic parenchymal failure (4%); (3) as obstruction of the inferior vena cava with symptoms referable to the liver appearing later (16%); (4) as hematemesis (3%); and (5) rarely as cachexia and pain from primary hepatic carcinoma dominating the picture (1%). Ascites appears in 93% of cases, hepatomegaly in 70%, epigastric pain in 54%, edema in 56%, and distended abdominal veins in 55%. Splenomegaly and jaundice are found in 30 and 28% respectively. The majority of cases proved fatal, and there is little evidence to suggest that recovery from occlusion of the major hepatic veins occurs, once symptoms have been produced. Hepatic parenchymal failure and surgical shock are among the immediate causes of death.

At the London Hospital the autopsy incidence of symptomatic hepatic vein occlusion was 0.061%, in that 18 cases were detected among 29,720 autopsies in which the liver was examined. The cause of the hepatic vein occlusion was established in 49 of 164 symptomatic cases (about 30%). In the remaining 115 symptomatic cases (70%), the cause was either unknown or inadequately established. The etiology of the occlusion was also known in most asymptomatic lesions. Of the known causes, polycythemia rubra vera, hypernephroma, and tumors of the inferior vena cava have been most frequently reported. In some of the cases of uncertain etiology, a general disorder of blood coagulation may have been present. In others, endogenous or exogenous toxins may have damaged the hepatic veins or led to thrombosis within them. Poisoning by pyrrolizidine (Senecio) alkaloids is discussed, but it is considered unlikely that these substances have been responsible for more than a very small proportion of cases.

Stenosis of the inferior vena cava accompanied the hepatic vein occlusion in 30% of the idiopathic cases and in many of those with known etiology. Occlusion of the ostiums of the hepatic vein existed in 44% of the idiopathic cases, but in most of these cases more distally situated lesions also existed. While in most cases the vascular lesions are explicable on the basis of thrombosis alone, an initial endophlebitis cannot be excluded on morphologic grounds.

The acute stages of hepatic vein occlusion are characterized by centrilobular congestion and either destruction or atrophy of the centrilobular parenchyma. The acuteness of the lesion, as judged histologically, often correlates poorly with the length of the clinical history, and lesions of different ages are usually found at death. With long-standing obstruction, centrilobular and later diffuse fibrosis and regeneration, at first periportal and later nodular, appear. Finally, cirrhosis may develop. Seven cases of primary hepatic carcinoma complicating hepatic vein occlusion have been reported.

The spleen is enlarged in about 25% of cases with hepatic vein occlusion. Evidence of portal hypertension has been reported. Secondary thrombosis of the portal veins occurs in about 20% of cases. After occlusion of the hepatic veins, alterations in the intrahepatic blood flow may occur, and the possibility of retrograde flow in the portal veins is discussed.

Study of Pulmonary Alterations in Patients with Leukemia. E. Tortarolo, G. Büchi and S. Chiarle. Minerva med. **50**:3507-3523 (Nov. 3) 1959 (In Italian) [Turin, Italy].

The authors report on 64 patients with leukemia, in whom there were also pulmonary manifestations of the disease. Acute leukemia was present in 28 patients, the chronic myeloid variety in 16, and the chronic lymphatic variety in 20. There were lesions in the parenchyma of the lung alone in 44 patients (70%). Nodular masses were mostly observed in lymphatic leukemia, and thickened masses in the acute variety. The involvement of the pleura was mostly found in lymphatic leukemia, and thickening of the base of the lung in the myeloid variety.

Histological examination of the material obtained from 10 patients at autopsy revealed enlargement of hilar and mediastinal lymph nodes in 5 instances, hemorrhagic areas in 3, diffuse thickening of the lung tissue in 4, edema in certain parts of the lung in 3, presence of enlarged nodules and nodes in 8, and vascular thrombosis of the medium-caliber vessels in 1. There were some indications that the pulmonary manifestation of systemic leukemic disease in a few instances set in early. However, the timing of the pulmonary manifestation in most patients could not be demonstrated.

SURGERY

Pituitary Tumors in Patients with Cushing's Syndrome. R. M. Salassa, T. P. Kearns, J. W. Kernohan and others. J. Clin. Endocrinol. **19**:1523-1539 (Dec.) 1959 [Springfield, Ill.].

Presence of pituitary tumor either before or after adrenalectomy was indicated by roentgenologic findings at the Mayo Clinic in 12 of the 122 patients who had adrenocortical hyperfunction (Cushing's syndrome) associated with adrenocortical hyperplasia. The group included 9 women and 3 men, and the ages varied from 21 to 60 years. Cushing's syndrome was severe in 8 patients, moderate in 1, and mild in 3. The duration of the illness varied from 1 to 10 years in 10 of the patients; the disease had developed in the other 2 patients within a period of 4 months before the examination. The urinary excretion of corticosteroids was above normal in each of the 12 patients, and the urinary excretion of 17-ketosteroids was increased in 5. Microscopic examination of the pituitary tumor was carried out in 7 of the 12 patients, and it demonstrated that all lesions were chromophobe adenomas. One tumor was malignant with extracranial metastatic lesions, but the other 6 showed no clear histological evidence of malignancy. Six patients had ocular disorders. Five patients had defects in the visual fields, 3 of them having involvement of motor nerves to the eye. One patient had paralysis of the 3rd, 4th, 5th, and 6th cranial nerves without involvement of the visual pathways.

The occurrence of pituitary tumor, sufficiently large to cause enlargement of the sella turcica in this group, suggests that there is likely a causal relationship of the pituitary tumor to Cushing's syndrome. Nine of the 12 patients had some clinical evidence of a pituitary tumor before adrenalectomy. The clinical course of 5 patients treated by total adrenalectomy and of 3 of 5 patients treated by subtotal adrenalectomy suggested that adrenalectomy favored the development of the pituitary tumor. Cutaneous melanosis developed in 8 of the 10 patients who survived adrenalectomy for more than 3 months. Its persistence despite adequate or excessive replacement therapy with cortisone suggests an uncontrolled excessive secretion of some type of pigmentary hormone. The usual and effective treatment of Cushing's syndrome associated with adrenocortical hyperplasia at the Mayo Clinic during the past 14 years has been total or radical subtotal adrenalectomy, despite the possibility that the remote cause of the disease may reside outside the adrenal cortex.

Hypophysectomy in the Treatment of Breast Cancer. A. G. Jessiman, D. D. Matson and F. D. Moore. New England J. Med. 261:1199-1207 (Dec. 10) 1959 [Boston].

The authors report on 52 women and 1 man, between the ages of 32 and 69 years, who underwent hypophysectomy as part of their treatment for metastatic cancer of the breast at Peter Bent Brigham Hospital in Boston. Most of the patients had been treated previously with local x-ray and hormone therapy, and each of the patients had undergone castration. Total excision of the anterior pituitary body was the aim in every patient. The pituitary stalk was cut just above the gland, but was not clipped or cauterized. After extracapsular dissection of the gland it was possible in the last half of this series to remove the gland intact. Intravenous administration of 17-hydroxycorticosterone (compound F) was started at the time of stalk section and continued, so that 50 mg. was given by the time operation was completed. Intravenous administration of 17-hydroxycorticosterone was continued in the postoperative period, so that a total dose of 200 to 250 mg. was administered by this route during the first 24-hour period. Cortisone was administered in doses of 200 mg. per 24 hours the first 2 or 3 days after the operation, and then decreased at the rate of 25 mg. every second day until a maintenance level of 50 mg. per day was reached, usually in 7 to 10 days. All patients except one required maintenance treatment with U. S. P. thyroid in doses of 0.06 to 0.12 Gm. (1 to 2 grains) daily. This need for thyroid replacement did not appear for 5 or 6 weeks.

Among the 53 patients, in only one is it believed that life was shortened by the hypophysectomy. This patient had bilateral pulmonary and pleural disease and died of aspiration pneumonitis on the 7th postoperative day. The operative mortality thus was less than 2%. Clinical results have been reported on 45 of the 53 patients. Excellent results were obtained in 10 patients (22%), with an average duration of remission of 12 months and an average survival period of 15 months. By excellent is meant a significant measurable regression in the disease with demonstrable healing of metastatic lesions. Fair results were obtained in 17 patients (38%), with an average duration of remission of 6 months and an average survival period of 11 months. By fair is meant obvious halting of the natural progress of the disease, with no detection of new lesions. Poor results, with not alteration in the progressive worsening of the patient's condition or with a temporary halt in the growth of some lesions accompanied by simultaneous appearance of new lesions, were obtained in 18 patients (40%), with an average survival period of 3½ months. The course of the disease thus was favorably altered in 27 patients (60%). Two additional women in whom the disease developed during pregnancy were treated by hypophysectomy. Both women delivered normal infants; one patient died subsequently of causes unrelated to hypophysectomy or to carcinoma of the breast; the other patient died of the disease one month after the delivery.

The results obtained suggest that prolongation of the patient's life and symptomatic relief during this period of remission will best be served when hypophysectomy is employed in treatment of early metastatic spread of cancer of the breast as opposed to diffuse or terminal disease. The most favorable patient for hypophysectomy appears to be a woman who is less than 10 years postmenopausal, with disease involving the skin, lymph nodes, skeleton, or lung, but not the brain, liver, or the viscera generally, who has good cardiac, renal, and pulmonary function, and who has responded well to castration or had some other evidence of a hormone-sensitive tumor. The endocrine changes resulting from the operation are related both to the completeness of the procedure and to the subsequent clinical course of the patient. The significance of the observed resurgence of estrogenic activity with exacerbation of the disease is discussed. Surgical hypophysectomy has become a safe procedure and a valuable addition to the methods of therapy available in the treatment of advanced cancer of the breast.

Traumatic Infarction of the Anterior Lobe of the Pituitary Gland. P. M. Daniel, M. M. L. Prichard and C. S. Treip. Lancet 2:927-930 (Nov. 28) 1959 [London].

The authors, having been unable to find a description of an acute massive lesion of the anterior lobe of the pituitary gland caused by trauma, record 5 cases in which extensive infarction of the anterior lobe, due to rupture of the pituitary stalk, was found at autopsy shortly after head injury. A 6th case is recorded which showed the reverse picture —i. e., an anterior lobe without infarction despite a traumatic rupture which had separated the pituitary from the hypothalamus. In all these cases the pituitary was embedded in paraffin, and serial sections were cut.

The authors believe that, in the 5 patients in whom the infarct in the anterior pituitary was large, the infarction was due to rupture of the pituitary stalk at the time of the accident. Their reason for this belief is that the extent and situation of the infarct, together with the disribution of the small areas of surviving anterior-lobe cells, provide a picture which is remarkably similar to that which they observed in the pituitaries of patients who survived for only a short time after surgical pituitary-stalk section. Moreover, they saw essentially the same picture of extensive anterior-lobe infarction in laboratory animals killed shortly after pituitary-stalk section.

The anterior lobe is supplied solely by the hypophysial portal vessels, which arise in and run down the free part of the pituitary stalk. These are inevitably interrupted when the stalk is severed, and thus an extensive area of ischemic necrosis develops, mainly centrally, in the anterior lobe. A relatively small area of the anterior lobe, adjacent to the neural tissue, survives, because this area is supplied by the short portal vessels which arise in the lower infundibular stem (a continuation of the neural tissue of the stalk, which is actually embedded in the anterior lobe).

The 6th case, in which the anterior lobe of the pituitary was not infarcted, provided interesting information about the blood supply of the pituitary stalk and the anterior lobe. The pituitary stalk region was carefully examined. The stalk itself was found to be intact and continuous below with the pituitary, but its upper extremity had been torn away from the hypothalamus. As a result of the high level of the tear, the primary capillary bed and the portal vessels within the stalk were undamaged. The superior hypophysial arteries supplying the stalk were intact. Thus, the trauma which had produced separation of the pituitary from the brain had not interrupted the blood supply to the anterior lobe of the pituitary.

Dermoid Cysts of the Nose: A Review of 39 Cases. C. C. Nydell Jr. and J. K. Masson. Ann. Surg. **150**:1007-1016 (Dec.) 1959 [Philadelphia].

The authors review the literature on dermoid cysts of the nose and the 39 cases seen at the Mayo Clinic from 1915 to 1956 inclusive. The etiology of the dermoid cyst of the nose is closely involved in the embryologic development of the nose. Although the lesion is rare, recognition and differential diagnosis of it are not difficult. Treatment, however, has tended to be inadequate.

Among the 39 Mayo Clinic cases, male patients outnumbered female 23 to 16. In 23 cases the deformity had been noted at birth and had progressed. In 7 cases the time of onset was uncertain, which suggests that the cyst may have presented early in life. The commonest presenting complaints were swelling and a discharge. Despite the early appearance of the lesion, very few patients received definitive treatment early in life. The ages at which treatment was sought at the clinic ranged from 5 months to 51 years. In 26 cases a history of previous surgical treatment was obtained. In others, treatment with salves, caustics, and antibiotics had given inadequate results. In 2 of the 39 cases saddle-nose deformities developed, which necessitated subsequent plastic repair.

Treatment at the Mayo Clinic in the earlier cases was destruction of the cyst-lining epithelium by excision, or frequently by electrocautery. In the last decade the trend has been toward thorough anatomic dissection and total excision of the cyst, and primary closure of the defect. Complete excision, the optimal treatment for congenital dermoid cysts, means removal of all remnants, ramifications, and fistulas, for the cyst will recur if removal is not complete. Some cases are matters of simple excision; others require extensive dissection. Outlining of the tract and cyst with dye may simplify the task of finding all remnants. Facial deformities secondary to the extensive surgical measures sometimes necessary, or those caused by the growth of the cyst itself, may be corrected at the primary procedure or at a later date. If the supporting structures are missing, the use of local flaps or grafts of cartilage or bone, or a combination of these measures, may be required.

Cervical Diskography: A Contribution to the Etiology and Mechanism of Neck, Shoulder and Arm Pain. R. B. Cloward. Ann. Surg. **150**:1052-1064 (Dec.) 1959 [Philadelphia].

Cloward points out that diskography was first used by Schmorl in 1929, and was presented for clinical diagnosis by Lindbloom in 1948. Surgeons have been reluctant, however, to accept it as a routine diagnostic procedure because of fear of injury to a normal disk. Nevertheless, it has been used at the author's clinic in Honolulu in the diagnosis of ruptured lumbar disks since 1950, and more than 450 lumbar diskograms have been made during the ensuing 8-year period. Information obtained from this study of lumbar disks was a stimulus to the development of a similar procedure for cervical disks, and in the last 3 years 114 patients have been subjected to cervical diskography.

In performing cervical diskography, a needle is inserted into the intervertebral disk from its anterolateral surface. By applying deep digital pressure between the trachea and carotid artery, the anterior surface of the vertebral bodies can be palpated easily at a depth of less than 1 cm. the 2-needle technique is used: The first needle, a no. 20, 2 in.

long, is inserted diagonally into the outer anterolateral fibers of the annulus fibrosus of the disk; through this guide a second fine 2½-in. (no. 25) needle is inserted into the center of the nucleus pulposus. The positions of the needles are determined radiographically. Only 0.2 to 0.3 cc. of a radio-opaque solution can be injected into a normal cervical disk. The procedure is carried out in the x-ray room. A small amount of Novocain in the skin is the only anesthetic used. Since the patient is conscious and cooperative, he can inform the operator as to the location of pain when the needles are inserted and the injection made.

By injection of the disk for diskography and by stimulation at operation, the origin of referred pains has been determined. Sensory nerve endings in the lower cervical intervertebral disks and their ligamentous confines have been shown to be responsible for the clinical symptoms of pain in the neck, scapula, shoulder, and upper arm. Conspicuous by their absence were pains radiating into the precordium or suboccipital region, headaches, and pains referred to the face and jaw, all of which have been attributed to the cervical intervertebral disk. The author did not observe precordial pain as part of the cervical disk syndrome. In making cervical diskograms and stimulating the disk at operation, every patient has been asked if he experienced pain in the anterior surface of the chest. None has described or admitted to pain in this location.

The referred pains in the neck, shoulder, and upper arm are thought to be due to local reflex spasm (myalgia) of the muscles of the shoulder girdle. They are encountered in patients with acute injuries to the cervical spine (whiplash injury) or chronic cervical disk disease (spondylosis). They have their origin in the periphery of the cervical disk and the ligaments which surround it. Irritation of these sensitive structures is thought to be due to abnormal movement of the vertebral joint associated with cervical disk pathology. These symptoms can be relieved by arresting movement between 2 adjacent vertebral bodies. This is accomplished by a new surgical procedure, consisting of vertebral body fusion, by the anterior cervical approach.

Carcinoma of the Thyroid in Children. G. Crile Jr. Ann. Surg. 150:959-964 (Dec.) 1959 [Philadelphia].

Carcinoma of the thyroid, although fairly common in young adults, is rare in children. This report records the findings and responses to treatment in 18 consecutive cases of carcinoma of the thyroid in children, from 3 to 15 years of age. In 14 of the 18 children the parents were asked whether the children had received any form of radiation around the head and neck. Eleven had received radiation in the first 4 years of life—5 to the thymus as infants, 2 to the tonsils and adenoids, 2 to the skin for eczema, 1 to the mediastinum for enlarged nodes, and 1 to the cervical lymph nodes. The amount of radiation given was often very small. In the 15 years between 1924 and 1939, no children with cancers of the thyroid were seen at the Cleveland Clinic. Only 3 were seen between 1939 and 1950, but between 1950 and 1958 there were 15 cases.

In 14 of the 17 cases of papillary carcinoma, metastases in the cervical nodes were the leading sign of the disease. In 7 cases the primary tumor was occult. The papillary carcinomas in this series of children were more malignant than similar tumors are in adults; they invaded the thyroid more extensively, and metastasized more frequently and more extensively to lymph nodes and lungs. Treatment was individualized and included lobectomy, subtotal or total thyroidectomy, with unilateral or bilateral resection of grossly involved groups of nodes. Conventional radical neck dissections with sacrifice of sternocleidomastoid muscles were not employed; total thyroidectomy was not done unless all of the thyroid was involved; and most of the thyroidectomies and neck dissections were performed through transverse thyroidectomy incisions. Seventeen of the 18 patients are living, with an average survival time of more than 5 years. Since none of the patients with operable disease in this series has died of local recurrence or has evidence of persistent carcinoma in the neck, there seems to be no necessity of routinely performing either total thyroidectomy or the conventional radical neck dissection with removal of the sternocleidomastoid muscles. Most of the cancers of the thyroid which occur in children appear to be dependent on thyroid-stimulating hormone, and their growth can be at least partly controlled by the feeding of desiccated thyroid.

Surgical Aspects of Chronic Thyroiditis. C. J. Priebe Jr. and H. A. Patterson. Ann. Surg. 150:965-975 (Dec.) 1959 [Philadelphia].

Chronic thyroiditis was found in 44 of the 889 patients (about 1 in 20) who underwent thyroid surgery at Roosevelt Hospital, New York, in the 10-year period from 1947 to 1956. There were 20 cases of Hashimoto's type, 11 of Riedel's type, and 13 of an unclassified type. The first 2 types combined accounted for 31 (3.4%) of the total thyroid operations. These are the most important to the surgeon, for here the disease requires specific treatment, while in the unclassified type treatment is dictated by the associated pathological changes.

With regard to Hashimoto's type of chronic thyroiditis, the authors arrive at the conclusion that this type of thyroiditis should be suspected in any white woman with a diffuse goiter, discomfort in the neck, and a low basal metabolic rate. Diagnosis by frozen section is essential for the surgeon to evaluate a firm, diffusely enlarged gland, which is finely lobulated and tan on cross section. Operation is necessary for accurate diagnosis, for relief of pressure symptoms, and for cosmetic reasons. Bilateral thyroidectomy, consisting of resection of 50 to 75% of the gland, seems best to prevent recurrence, while preserving endocrine function.

Riedel's type of chronic thyroiditis is usually found in middle-aged women with recent, localized, firm thyroid enlargement. There may also be symptoms of neck pressure. At operation, a malignant thyroid tumor may be suspected because of hardness and adherence to surrounding structures. Diagnosis by frozen section is valuable, though not infallible. The surgeon should be conservative when distinction between carcinoma and thyroiditis is in doubt, because radical excision for chronic thyroiditis is a costly error. The amount of gland resected for chronic thyroiditis should not be greater than that required for accurate diagnosis and prevention of constriction. The unclassified type of chronic thyroiditis is essentially a secondary pathological process superimposed on an already diseased gland. It may simulate other types before operation, during operation, and on diagnosis by frozen section. Surgery is performed primarily for the associated lesion, and to rule out carcinoma. Resection in each case should be as conservative as the associated disease allows.

Experiences with Coarctation of the Aorta. C. P. Bailey, W. M. Lemmon and B. G. Musser. Am. J. Cardiol. 4:775-785 (Dec.) 1959 [New York].

While Bonnet's classification of aortic coarctation still has many adherents, the authors are of the opinion that it is inadequate to embrace all of the forms. Its primary basis is the division into the "adult" form, which is characterized by obliteration of the patent ductus arteriosus with extensive overdevelopment of a collateral arterial system, and the "infantile" form, in which there is little collateral development and the lower aortic segment is supplied with venous blood from the pulmonary artery by way of a patent ductus arteriosus. Yet, the "infantile" form may be seen in adults, and the "adult" form necessary must occur first in infants. Furthermore, a patent ductus may be present in the "adult" form.

The authors present the following new system of classification for coarctation of the aorta: Type 1 is the classically located coarctation with ligament (ductus arteriosus obliterated). Type 2 is the classically located coarctation with shunt; this type is subdivided into (*a*) ductus arteriosus present and patent to the upper aortic segment with left-to-right shunt and (*b*) ductus arteriosus present and patent to the lower aortic segment with right-to-left shunt. Type 3 is the coarctation with hypoplasia (usually of the entire descending aorta). Type 4 is the isthmus interruption; etiologically and pathologically, this condition differs from true coarctation in that a segment of the aorta actually is absent. Type 5 is coarctation occurring in an unusual location. The various types of oartic coarctation are illustrated in diagrams, and the surgical techniques used to overcome them are discussed.

The authors describe the results obtained in 58 patients operated on for coarctation of the aorta over a period of 9 years. Only one patient died in the hospital, making the surgical death rate 1.7%. Aspects of the surgical technique which permit rapid, safe, and adequate surgery are emphasized. Grafting was done less often than is usually the case. In 5 patients both aortic stenosis and coarctation of the aorta were found. In 3 of these patients the coarctated segment was removed and anastomosis performed, followed by transventricular aortic dilatation; these have done well. The other 2 patients had excision of the coarctated area and anastomosis alone; both of them subsequently died, one as a result of the valvular stenosis and the other because of complication of the required second operation. The rate of cure by operation for hypertension due to coarctation of the aorta is probably higher than for hypertension caused by any other condition. In 88% of the patients there was an immediate lowering of the blood pressure in the arms after the operation, and this has been maintained. All the patients followed up have excellent pulsations and/or normal blood pressures in the lower extremities.

The authors conclude that every practicing physician should have a high index of suspicion regarding the possibility of existence of coarctation of the aorta when confronted with a patient who presents with a systolic murmur and/or systemic hypertension. The diagnosis usually can be made by clinical examination in the physician's office. The anomaly is surgically curable, with an acceptable operative mortality and a high likelihood of a good clinical and physiological result if corrected early.

Prevention of Lymphoedema of the Arm in Radical Surgery of Cancer of the Breast. A. N. Canónico. Prensa méd. argent. 46:1666-1669 (June 26) 1959 (In Spanish) [Buenos Aires].

One hundred ten unselected women who had a radical mastectomy were managed by a certain scheme for preventing immediate postoperative lymphoedema of the homolateral arm. The preventive treatment consisted of (1) making an adequate incision so as to procure a resulting soft and flexible scar; (2) caution during the operation to prevent trauma to the axillary vein; (3) not using the homolateral arm for giving blood or blood serum transfusion; (4) administration of antibiotics during the first 3 days after the operation; and (5) placing the patient under care of the surgeon himself until the healing process had been completed. The homolateral arm was bandaged with a moderately elastic bandage, which was not removed for an entire week after the operation. The diet contained little salt and was low in calories. Diuretics were given to the patients, and small doses of thyroid hormone on certain indications.

Of the greatest importance for the prevention of immediate postoperative lymphoedema of the homolateral arm was the early establishment of postoperative kinesitherapy. Local massage and active and passive exercises were given only by a trained physical therapist. Muscular exercises, which were begun 24 hours after the operation, followed a slow progressive scale to obtain complete functional recuperation of the arm. Massage of the soft parts of the axilla, the shoulder, and the arm was started by the end of the first week after the operation and was continued for 4 or 5 weeks. When postoperative roentgenotherapy was indicated, it was given in association with kinesitherapy in order to prevent fibroretractile sequels.

A follow-up for more than one year showed excellent results in 102 patients (92%); the functional capacity of the homolateral arm was normal. Sixty-three patients in this series did not have lymphoedema of the homolateral arm at all; 39 patients had a mild degree of edema of not more than 2 cm., in the remaining 8 patients there was a moderate degree of edema of from 2.5 to 4 cm. Immediate postoperative lymphoedema of the homolateral arm after a radical mastectomy can be prevented by following the scheme described. Special importance is attached to kinesitherapy.

Bronchogenic Carcinoma: An Aggressive Surgical Attitude. J. M. Chamberlain, T. M. McNeill, P. Parnassa and J. R. Edsall. J. Thoracic & Cardiovas. Surg. 38:727-745 (Dec.) 1959 [St. Louis].

The authors report on 248 patients who were operated on for bronchogenic carcinoma during the period 1949-1958. Epidermoid carcinoma was present in 134 patients (54%), adenocarcinoma in 40 (16%), anaplastic carcinoma in 59 (24%), and bronchiolar carcinoma in 15 (6%). The sex incidence was 222 for men and 26 for women, a ratio of 8.5 to 1. "Standard" resection was performed on 120 patients, and "extended" resection on 33; the remainder had noncurative, palliative, and exploratory resections. Both standard and extended resections were considered potentially cured at operation. Surgical specimens of standard resection consisted only of pulmonary structures, parietal pleura when adherent, and mediastinal lymphatic tissue. Extended operation included removal of the extrapleural structures invaded by the carcinoma. The mean duration of the postoperative hospital stay was not increased significantly by extending the operation. There were 34 instances of operative complications. The most frequent of these were cardiorespiratory failure (6), bronchopleural fistula (5), empyema (4), hemorrhage (4), pulmonary embolus (3), and metastases (3). The complication rate for the extended operation was 30.2% (13 patients) compared with 13.4% (19 patients) for the standard operation. Hospital deaths numbered 23 (9.3%). The patients who had a standard operation have had a mean survival of 21.6 months at the time of writing; 36.7% of these patients are still living. The patients who had an extended operation have had a mean survival of 16.7 months; 50% of these patients are still living. Of 28 patients in the noncurative resection group, only one is living. Several years must pass before the customary 5-year survival data can be compiled. The trend of the preceding statistical data suggests that extended resection is not only justifiable, but is clearly indicated whenever it is technically feasible.

Scalenus Anticus Syndrome: Result of Operative Treatment of 20 Cases, Including 16 with Cervical Costae. P. Rasmussen and N. G. Simonsen. Nord. med. 62:1572-1573 (Oct. 29) 1959 (In Danish) [Stockholm].

Sixteen patients, 4 men and 12 women, with scalenus anticus syndrome were treated at the Aarhus District Hospital, in Denmark, from April, 1943, to April, 1957. In addition, 4 patients had bilateral symptoms which had developed at intervals in the course of several years, so that, in all, 20 patients were operated on. At the start of the disease the patients ranged in age from 15 to 50 years. On admission, the symptoms had lasted from less than a year to 10 years. Pain was the most frequent symptom. Of the 3 patients without pain, 1 had motor symptoms exclusively, and 2 had vascular symptoms exclusively. Scalenotomy was performed in the 20 cases. The cervical ribs were extirpated or resected in only 9 of the 16 patients with costa cervicalis syndrome. In 8 cases a fibrous string was cut. The time of observation averaged 4.6 years. Recovery or marked improvement resulted in 14 patients, and slight improvement followed in 4; there was no change in 2 patients. The results were best in the costa cervicalis group in which only scalenotomy was performed.

The Surgical Treatment of Cylindroma (Adenoid Cystic Carcinoma) and Muco-Epidermoid Tumors of the Bronchus. W. S. Payne, F. H. Ellis, L. B. Woolner and H. J. Moersch. J. Thoracic & Cardiovas. Surg. 38:709-726 (Dec.) 1959 [St. Louis].

One hundred sixty-two malignant tumors originating in the bronchial mucous glands were diagnosed at the Mayo Clinic from 1927 through 1958. Of these, 13 were cylindromas (adenoid cystic carcinomas) and 4 were mucoepidermoid tumors of the bronchus. There was no sex predilection. The symptoms were mainly those of bronchial dilatation or bronchial obstruction and pneumonitis. Roentgenologic studies demonstrated massive collapse of one entire lung in 4 patients with mucoepidermoid tumors and in 4 with cylindromas, also lobar collapse in 7 patients with cylindromas. There was no sign of abnormality in 2 patients at the time of diagnosis. The bronchoscopic description of a cylindroma was a polypoid infiltrative tumor; that of a mucoepidermoid tumor was a large polypoid endobronchial mass that completely obstructed a primary bronchus.

The gross specimen of lung containing the primary tumor was available for review in 7 of the 13 patients with cylindromas. All these tumors involved major bronchi, and none presented as a peripheral pulmonary lesion. At the margins of the gross tumors there was extensive subepithelial infiltration of the mucosa. They all showed deep penetration and peribronchial extension, with destruction of bronchial cartilages and invasion of neural elements. Microscopic sections of the 4 mucoepidermoid tumors showed that they were covered with metaplastic squamous bronchial epithelium. None of these 4 tumors showed destruction of cartilage or involvement of nerves, lymph nodes, blood vessels, trachea, mediastinal structures, or distant organs. Seven patients with cylindromas and 2 patients with mucoepidermoid tumors were treated surgically. At the time of follow-up study, 4 of those operated on for cylindroma were alive and well 1 to 13 years after treatment. Also, the 2 patients who were surgically treated for mucoepidermoid tumor were living and well 8 to 10 years after the operation.

The Surgical Treatment of Ulcerative Colitis. J. H. Garlock. Dis. Colon & Rectum 2:529-533 (Nov.-Dec.) 1959 [Philadelphia].

The markedly improved results of the surgical treatment of nonspecific ulcerative colitis over the past 20 years have been owing largely to the elimination of ileostomy complications and a better understanding of the physiological changes which occur after operations. Complete rehabilitation of patients after appropriate surgical procedures may be expected in the great majority of these cases. From his own experience with about 500 cases of ulcerative colitis and careful appraisal of results, the author points out that (1) acute fulminating disease, (2) severe, uncontrollable hemorrhage, (3) perforation with peritonitis, and (4) extensive polyposis with or without carcinoma are definite indications for surgical treatment. Other important indications for surgical intervention are concerned with the pathological complications of colitis, comprising mainly pericolonic and extrarectal extensions; they are abdominal wall abscess and fecal fistula, rectovaginal fistula, and internal fistula.

The author points out that the routine use of proctocolectomy in one stage for all cases of ulcerative colitis is to be deprecated, mainly because this removes forever the possibility of reestablishment of intestinal continuity. The problem of reconnection, i. e., ileorectal anastomosis, demands serious consideration. It is extremely doubtful whether this operation should be carried out in the presence of active disease in the rectum or any rectal complications, such as fistula, anal incontinence, polyposis, and stricture. There is urgent need for individualization and careful appraisal of each patient.

Gastrectomy for Massive Gastrointestinal Haemorrhage of Unknown Cause. J. Bruce and H. A. F. Dudley. Lancet 2:992-994 (Dec. 5) 1959 [England].

The authors report on 19 men and 12 women, between the ages of 20 and 80 years, with massive gastrointestinal hemorrhage, in whom an obvious lesion was not present on external examination or on palpation of the stomach and duodenum, and who underwent a standard two-thirds to three-quarters gastrectomy ("blind" gastrectomy) in the surgical units of the Edinburgh Royal Infirmary and the Western General Hospital in Edinburgh. Of the 31 patients, only 3 were aged less than 40 years. In 7 patients the operation was performed within 24 hours of admission; in 9, it was delayed up to 2 days, and in 15, from 2 to 10 days. In all the patients there was no obvious evidence of an active peptic ulcer at laparotomy. In 6 patients it was considered that there might possibly be a healed ulcer, but pathological confirmation in the resected specimen was obtained only once. Superficial gastric ulcers or gastric erosions, thought to be the cause of the hemorrhage, were found in 19 specimens, and a duodenal ulcer, in 2. Microscopic examination suggested that the line of section had passed through an ulcer of the lesser curvature of the stomach in 1 patient, and in another an unresected ulcer was found in the duodenal stump. The remaining 2 patients had large hiatus hernias; the resected specimen of one of them contained a superficial gastric ulcer, but in the other a cause of bleeding was not found. Gastrotomy was carried out only once and revealed a superficial gastric ulcer. There were 3 deaths—one from intractable paralytic ileus; the second from repeated hemorrhage owing to a small anterior ulcer in the duodenal stump, which had not been detected at the gastrectomy; and the third from a pulmonary embolus.

Many patients with gastrointestinal bleeding of unknown causation, whose bleeding is less severe, may recover with medical treatment. Results in the 31 patients suggest, however, that lack of a clear history of digestive upset does not preclude the existence of a superficial ulcer, usually gastric but occasionally duodenal, from which fatal bleeding will occur if gastrectomy is not performed. The delay of gastrectomy in the 31 patients reflects the natural unwillingness of both physician and surgeon to submit a patient to surgical treatment without good evidence of the cause of the bleeding. A subtotal gastric resection will remove the lesion in 75% of the patients and will arrest the bleeding in most of the remainder. The over-all mortality in this group should be no more than 10%. If massive bleeding continues after gastrectomy, only reoperation is likely to save the patient.

Surgical Implantation of Hodgkin's Disease of the Stomach to the Skin of the Abdominal Wall. F. C. Jackson, E. C. Ney and E. R. Fisher. Ann. Surg. 150:1000-1006 (Dec.) 1959 [Philadelphia].

The patient was a 47-year-old man who was first seen in September, 1954, complaining of postprandial epigastric pain and a loss in weight of 33 lb. (15 kg.) over the preceding 3 years. The radiologist's impression was "hypertrophic gastritis" with a "polypoid mass." Laparotomy revealed an infiltrating tumor of the fundus and greater curvature of the stomach extending almost to the pylorus. After extending the incision into the chest, a biopsy of the fundus was taken where tumor invaded the serosa. The pathologist's diagnosis on frozen section was "malignant lymphoma." Total gastrectomy, omentectomy, splenectomy, and resection of the tail of the pancreas were performed with a loop esophagojejunostomy and distal enteroenterostomy. Microscopic examination of the surgical specimen revealed that much of the gastric mucosa was replaced by malignant neoplasm, a polymorphous infiltrate of reticulum cells, plasma cells, and lymphocytes. Many reticulocytes were atypical and exhibited frequent mitoses. Multinucleated forms of the Reed-Sternberg cells were also seen. Sections from lymph nodes, spleen, and pancreas revealed no neoplasm.

On the 11th postoperative day an abscess appeared at the costal margin of the wound, which was drained. Postoperatively, 10 mg. of nitrogen mustard was administered intravenously every other day for 4 doses—a total of 1.4 mg. per kilogram. A draining sinus was still present when the patient was discharged. When he was readmitted 3 months later, the edges of the defect were excised. Sections of the abdominal skin revealed a dense infiltrate of the upper corium, as well as focal areas of the subcutaneous tissue and periappendageal tissues, by plasma cells, lymphocytes, occasional eosinophils, and moderate numbers of reticulum cells. Many of the latter appeared atypical, and occasional giant cells of the Reed-Sternberg type could be identified. A total of 2,400 r (air dose) of radiation was delivered to the old area of the wound sinus in a period of 15 days. After that the wound healed. In 1957, because of tryptic esophagitis, the loop jejunostomy was converted to a Roux-en-Y esophagojejunostomy. This procedure permitted a "second look." No gross tumor was found in organs or lymph nodes. The patient is alive and well 3 years and 6 months after excision and local radiation to the site of implantation and almost 4 years after removal of the primary gastric tumor. This is the first reported instance of implantation of Hodgkin's disease of the stomach. It is suggested that with increase in surgical treatment of unifocal Hodgkin's disease other instances may be reported in the future.

The authors cite the following factors as evidence of implantation: 1. The tumor barrier was violated during operation by direct biopsy. 2. The characteristic morphologic appearance of Hodgkin's granuloma with Reed-Sternberg cells was demonstrated in the wound. 3. The patient had no other manifestations of Hodgkin's disease in the skin. 4. Studies on the scalene and axillary lymph nodes more than 2 years later revealed no evidence of Hodgkin's disease, and indicated that the stomach lesion was unifocal.

Treatment of 126 Cases of Malignant Melanoma: Long Term Results. S. L. Gumport and H. W. Meyer. Ann. Surg. 150:989-992 (Dec.) 1959 [Philadelphia].

While up to 1940 the general impression was that treatment was of little or no value in malignant melanoma, more recent reports indicate that this is no longer true. This report is concerned with 126 of the 192 patients who were operated on for malignant melanoma by members of the tumor service of New York University postgraduate medical school at University Hospital, New York, since 1944. In these 126 patients more than 5 years have elapsed since the surgical treatment. All diagnostic and therapeutic procedures took into account the ease with which a melanoma may spread by way of either the blood stream or the lymphatics. In the presence of a pathognomonic lesion, biopsy was omitted. The entire lesion was removed as a total excision biopsy, rather than an incisional biopsy, when biopsy was deemed necessary.

Surgery consisted of wide and deep excision of the primary lesion, including the underlying fascia, and grafting was usually necessary. The regional lymph nodes were removed in continuity whenever it was technically feasible. Gentle handling of the tissues and sterilization of instruments after each individual use were emphasized in order to prevent implantation. The use of sharp retractors and of local anesthesia was avoided for the same reason. When it was not practical to remove the regional lymph nodes in continuity, they were removed several weeks later, after the site of the primary lesion was well healed. The removal of the regional lymph nodes should not be postponed until they are grossly involved. When there was clinical evidence of involvement of the nodes, triethylene thiophosphoramide was administered at the time of operation. The same substance or phenylalanine mustard was administered when the disease had advanced to inoperability.

Dissection of the nodes was not carried out in 41 of the 126 patients. Of these, 11 are living and well, 8 could not be traced, and 22 either have died or have had recurrence. The best results were obtained in the 40 patients in whom lymph nodes were removed which were both clinically negative and microscopically free of tumor; 52% of these patients lived 5 years or more. However, even when the nodes were microscopically positive, 46% of the patients survived 5 years or more if the nodes had been clinically thought to be free of tumor. The 5-year survival rates dropped precipitously when the nodes were clinically involved.

NEUROLOGY & PSYCHIATRY

Cerebellar Atrophy with Oculocutaneous Telangiectasis and Bronchiectasis as a Familial Syndrome. A. Biemond and J. H. van Bolhuis. Nederl. tijdschr. geneesk. **103**:2253-2258 (Nov. 7) 1959 (In Dutch) [Amsterdam].

The authors present the case histories of 4 children, coming from 2 unrelated families. The first 2 were girls, born in 1940 and 1944, respectively; the other 2 were boys, born in 1944 and 1948. Both of he girls died, one at 17 years of age, and the other t 12. Autopsy studies were done on the younger of the 2 girls and on one of the boys, who died at 12 years of age. All 4 children presented a characteristic, progressive syndrome, consisting of cerebellar ataxia, later complicated by choreoathetosis; recurrent and chronic respiratory infections resulting in bronchiectasis; and telangiectasis, at first limited to the bulbar conjunctiva, but later developing in regions of the skin. Autopsy revealed bronchiectasis and diffuse fibrosis in the lungs. Clubbing of the fingers was also noted. The marked cerebellar atrophy was mainly confined to the vermis cerebelli.

The development of neurological disorders in these children with recurrent respiratory infections and the development of telangiectatic lesions in the bulbar conjunctiva had impressed van Bolhuis as a special syndrome some years ago. The difficulties encountered in the evaluation of the gradually developing neurological aspects led to neurological studies on the 4 children by Biemond in 1954. At this time the children were also examined by an ophthalmologist. The study was completed in 1956 when autopsies were performed on 2 of the children.

Biemond made a report on this syndrome at the International Neurological Congress in 1957. During the same year and in 1958 several reports of this syndrome appeared in the American and British literature, a total of about 20 cases having been reported so far. The authors feel that the term "ataxia-telangiectasia," applied to the syndrome by American authors, while practical, has the disadvantage of giving an incomplete description of the very characteristic triad; moreover, it suggests that the cerebellar lesion is the result of (cerebellar) telangiectasis, which is not the case.

Agranulocytosis During Treatment with High Doses of Chlorpromazine: Report of Case with Recovery and Review of Literature. F. O. Bastos, H. M. Carvalho and C. R. M. Arantes. Rev. Hosp. clin. **14**:300-311 (Sept.-Oct.) 1959 (In Portuguese) [São Paulo, Brazil].

A patient with paranoic schizophrenia of 4 years' duration was hospitalized at the psychiatric clinic of the Faculty of Medicine, University of São Paulo, Brazil. Previous treatment consisted of electroshock or insulin shock therapy, which had given the patient temporary relief. Neurological examination and laboratory tests (cerebrospinal fluid and basal metabolism) gave normal results. Chlorpromazine therapy was instituted by the "impregnation technique," starting with a dosage of 75 mg. daily during 3 days and increasing it gradually until it reached 2,400 mg. during 5 days. On the 55th day of treatment the patient developed fever, diarrhea, and vomiting. He was given sulfaguanidine and injections of Dibiotyl (penicillin and dihydrostreptomycin). The following day, as his condition was worse, the dose of chlorpromazine was reduced to 1,600 mg., and several laboratory and roentgenographic tests were performed. The hemogram showed agranulocytosis, with 700 leukocytes per cubic millimeter, 5% neutrophils, and 84.5% lymphocytes. The chlorpromazine treatment was suspended and a new therapy instituted, with administration of crystalline penicillin, whole blood transfusion, liver extract, vitamin B complex and vitamin B_{12}, plus isotonic sodium chloride solution and hypertonic dextrose solution. The patient recovered within a month from the onset of the toxic condition. This is the 54th case in the medical literature reviewed by the authors. The mortality in this reviewed series is 27.8%, with death occurring within 2 to 12 days after the onset of agranulocytosis.

Cerebral Thrombophlebitis in Children: A Clinical and Electroencephalographic Study. G. Carels and J. Henneaux. Acta paediat. belg. **13**:253-278 (no. 5) 1959 (In French) [Brussels].

Three cases of cerebral thrombophlebitis in children are reported. The course of the disease was documented by electroencephalograms taken periodically. Each of the 20 electroencephalograms taken for each patient was confronted with the clinical picture present at that particular phase, and thus the lesion was correctly localized after the start of the disease. The patients were 2 boys, aged 13 and 7 years, respectively, and one 11-year-old girl. In the first patient a meningitis syndrome, with crises of jacksonian epilepsy, had a sudden onset after a fall, during the course of an acute rhinopharyngitis and maxillary sinusitis. In the second patient a meningitis reaction, with total monoplegia of the left lower extremity, occurred during the course of a right ethmofrontomaxillary sinusitis. In the third patient a mild meningitis syndrome, with motor aphasia and right hemiplegia, occurred in the course of whooping cough. The diagnosis in the 3 patients was thrombosis of the rolandic vein. The treatment consisted of the intravenous administration of broad-spectrum antibiotics in massive doses, anticoagulants (heparin being administered successfully to one patient), hypertonic sodium chloride solution, and procaine. The 3 patients recovered within one month.

The prognosis in cerebral thrombophlebitis of children depends on early treatment, which requires an early diagnosis. Intense and early disturbances of consciousness have an unfavorable prognostic meaning. Electroencephalograms should be taken periodically for early localization of the lesion and for differentiation between cerebral thrombophlebitis and cerebral tumors or vascular malformations. Anticonvulsive treatment is in order even before the onset of any convulsive manifestation, and it should be maintained for some time after the clinical recovery. Infections, even if not suppurative, may be the source of cerebral thrombophlebitis. An investigation of such infections, which sometimes are moderate and undetected, should be part of the routine examination whenever a clinical picture of headache and malaise is followed by neurological symptoms.

PEDIATRICS

Study of Chronic Tetany in Late Childhood. H. P. Klotz and S. Tomkiewicz. Semaine hôp. Paris 35: 3239-3253 (Nov. 28) 1959 (In French) [Paris].

The authors report 20 cases of chronic tetany in older children and adolescents. The most frequent behavior signs and symptoms in the 20 patients were fits of rage, enuresis, nightmares, fainting, and spasmodic sobbing, and in 9 of them these behavior problems required special care. Trophic and somatic signs were defects of dental enamel and endocrine cataract. The prognosis is more favorable when the cataract is an isolated sign or when it appears in the midst of a polydystrophic tetany. Although the different forms of so-called idiopathic tetany of late childhood represent varieties of the same disturbance of calcium metabolism with several transitional types, 3 groups can be distinguished from the therapeutic and the prognostic points of view. The authors offer the following classification: 1. Chronic hypocalcemic tetany or idiopathic hypoparathyroidism. This is a rare condition and carries an unfavorable prognosis except when treated early. 2. Chronic normocalcemic or constitutional tetany. This is a frequently observed condition which carries a favorable prognosis and requires treatment only during periods of decompensation. 3. Multidystrophic chronic tetany or pseudohypoparathyroidism, which is frequently accompanied by serious mental disturbances and irreversible epilepsy.

It is the resistance to treatment and the prognostic value that constitute the main interest in distinguishing between the various clinical forms of chronic tetany in late childhood. The essential value of an early diagnosis is the possibility of curing, preventing, or minimizing a number of disturbances by means of a simple vitamin and calcium therapy. The presence of convulsions, of behavior or mental disorders, and of an incipient cataract in a child calls for an investigation of the familial background, for an electromyographic study, and for determination of calcemia and phosphoremia.

Kernicterus in Premature Infants. B. Yoffer, J. E. Howard, I. Ebensperger and others. Rev. chilena pediat. 30:205-213 (Sept.) 1959 (In Spanish) [Santiago, Chile].

A study of kernicterus not associated with hemolytic disease was made at the center for premature children of the Luis Calvo Mackenna Hospital in Santiago, Chile. The records of the premature infants who died of kernicterus without hemolytic disease, between 1956 and 1958, were compared with the records of 100 premature infants who entered the center during the same period. The 2 groups were analyzed in relation to obstetric circumstances, weight at birth, medication received (vitamin K and antibiotics), clinical picture, and laboratory tests (bilirubinemia and blood count). The 16 infants who died of kernicterus represented 1.6% of the 969 premature infants who entered the hospital and 6.6% of the total number of deaths at the center during the 2-year period studied.

Blood groups were compatible in 13 of the 16 infants in the kernicterus group, although there was a possibility of incompatibility in 3 of them. A definite correlation was found between the weight at birth and the incidence of kernicterus, represented by a frequency of 56.25% among all the infants weighing from 1,000 to 1,500 Gm. (approximately 2 to 3½ lb.) at birth, who were registered at the center during the period in study. Seventy-five per cent of the infants in the kernicterus group and 52% of those in the control group received vitamin K. The authors call attention to the fact that the highest rates of bilirubinemia were found among the infants who did not receive vitamin K, or who received it in lower doses. It was also found that, although the average maximum level of bilirubinemia in the kernicterus group (14.5 mg. per 100 cc.) was higher than the average maximum level in the control group (11.8 mg. per 100 cc.), hyperbilirubinemia was not necessarily associated with the disease. One infant in the kernicterus group had a bilirubinemia level of 6.8 mg. per 100 cc. on the 5th day of life. Seventy-five per cent in the kernicterus group and 50% in the control group received antibiotic therapy (sodium penicillin in doses of 100,000 units per kilogram of body weight over a period of 72 hours). Gastric aspiration, which was part of the routine examination at the center for premature infants, yielded abundant fluid and blood only from the 6th day on, associated with jaundice and neurological signs.

The pathological study of the infants who died of kernicterus confirmed the characteristic yellow impregnation of the cerebral nuclear masses, which may be associated with intracranial and pulmonary hemorrhage. The study showed that kernicterus is a disease of the small premature infant, and that an early diagnosis is very difficult.

Hemolytic Disease of the New-Born: An Analysis of Family Histories and Serological Findings. R. J. Walsh and H. K. Ward. Australasian Ann. Med. 8:262-266 (Nov.) 1959 [Sydney, Australia].

A sample of blood was collected for titration from 395 immunized women. Titers of the complete antibody were measured against D-positive red blood cells suspended in isotonic sodium chloride solution, and titers of the incomplete antibody against D-positive red blood cells suspended in 10% polyvidone solution. A history of pregnancies, including miscarriages, and of transfusion was obtained from each patient. Four categories, descriptive of the degree of severity of the hemolytic disease affecting children of these women, were established: (1) mild disease (the infant had not received any transfusion); (2) severe disease (transfusion treatment with recovery); (3) severe disease (transfusion treatment with death of the child); and (4) stillborn infant.

One hundred seventy-five women had not had another pregnancy after the first affected child, at the time of the examination. Thirty-one (approximately 14%) of the 220 children born after a first affected child were unaffected by Rh immunization. The highest percentage of unaffected children (19.6%) was found in the group in which the first affected child had experienced a mild form of hemolytic disease; the highest percentage of stillborn infants (44.6%) was found in the group in which the first affected child had also been a stillborn. It was also found that 34.2% of the first, 49.4% of the second, 51.3% of the third, and 45.7% of the fourth affected children died, which indicates no progressive increase in mortality. No correlation was found between the mother's parity and the degree of gravity of the hemolytic disease in the first affected child.

Although the severity of the disease increased with the mean titer of antibody, there were many exceptions to this picture, as indicated by the finding of 30 mildly affected infants associated with maternal titers of 256 or more, whereas 5 stillborn infants were associated with titers lower than 16. The effects of immunization by a blood transfusion were similar to those of immunization after a pregnancy, as indicated by the fact that the frequency of stillbirths was not significantly greater when immunization followed a transfusion. The most definite conclusion is that, if the first child is mildly affected, the subsequent children are more likely to survive than to die; the severely affected first born is more likely to be followed by a stillborn or a fatally affected infant.

PATHOLOGY

Primary Dissecting Aneurysm of Peripheral and Pulmonary Arteries: Dissecting Hemorrhage of Media. A. G. Foord and R. D. Lewis. A. M. A. Arch. Path. 68:553-577 (Nov.) 1959 [Chicago].

The authors report on 17 patients with primary dissecting aneurysm of peripheral or pulmonary arteries, in whom one or more arteries were involved. Only 2 patients were younger than 52 years. Hypertension was present in 12 patients. Direct traumatic injury of the involved artery took place in 2 patients. The renal artery was involved in 7 patients. There was involvement of the left anterior descending coronary artery in one patient, with fatal outcome. The superior mesenteric artery was involved in 3 patients; this artery was markedly narrowed, causing infarction of a long segment of the small intestine in 2 patients, and a branch of the superior mesenteric artery was involved in one patient. The other arteries involved in this series were: celiac, splenic, hepatic, and branches of left gastric (1); common hepatic (1); pulmonary, main and right (1); branch of right pulmonary (1); left common carotid (1); and left superior thyroid (1).

Dissection of the entire circumference of the artery involved was observed in 5 patients. Thrombosis in the lumen of an artery in which a dissecting aneurysm had developed took place in 2 patients. Infarction of the artery was present in 6 patients. Dissecting aneurysm appeared to have played a major role in causing death in 8 patients. The authors also collected 31 cases which had been reported in the literature. The conclusion is that there is no evidence of a lesion which is specific for peripheral arteries subject to dissecting aneurysm.

BOOK REVIEWS

The Viruses: Biochemical, Biological, and Biophysical Properties. Volume 1: General Virology. Edited by F. M. Burnet and W. M. Stanley. Cloth. $16.50. Pp. 609, with illustrations. Academic Press, Inc., 111 Fifth Ave., New York 3; Academic Press, Inc. (London) Ltd., 40 Pall Mall, London, S. W. 1, England, 1959.

Scientists who are tempted to study viruses today must be prepared to have a little knowledge of zoology, genetics, biochemistry, biophysics, microbiology, immunology, and, if they choose to become "quantifiers," mathematics. Up to now, they had to study textbooks of the respective disciplines in order to be versatile enough to find their way in virology; however, this book should make their lives easier. Instead of studying books on physics and biophysics, the future virologist will have the pleasure of reading chapter 3, which contains a brief, lucid, and informative account of Schachman and Williams dealing with the physical properties of the infective virus participles. This material should provide him with a sufficient background of physics to enable him to approach his problems in this field in an intelligent manner.

Pursuing further the application of biophysics to the knowledge of viruses, Schwerdt, in chapter 4, describes methods of counting virus particles and discusses the relationship between the physical count and the biological function of the virus particles. The major part of the book is devoted to the chemistry of viruses and the biochemical problem faced by a cell infected by a virus.

In chapter 6, Fraenkel-Conrat describes his study on the determination of the chemical structure of a tobacco mosaic virus, which belongs to the group of viruses that affect plants, as well as the results of pioneering studies conducted by Schram and coworkers at Tübingen. Pursuing the same theme, Bergold, in chapter 9, describes the biochemistry of insect viruses. The chemistry of bacterial viruses (bacteriophages) and animal viruses is analyzed in chapters 7 and 8 by Evans and Schafer respectively. Attempts are made in these two chapters to link the functional activity of viruses with their chemical composition or with what is known about their chemical structure.

One of the most important and well-written parts of the book is chapter 2, in which Seymour Cohen turns to the almost forgotten partner of virus infection, the host, and describes the intricate system of metabolic processes that take place in a normal cell and in one invaded by a virus. In chapter 11, Luria discusses the problem of viral genetics, which assumes a paramount role in the study of viruses, and the question of reproduction of bacterial, plant, and animal viruses. More practical aspects of virology are discussed in chapter 10 by Burnet. He describes different immunological reactions used to characterize viral properties.

Gard and Maaløe, chapter 5, deal with the problem of inactivation of viruses. The editors have provided an admirable introduction to the problems of virology. The book is primarily for graduate and young postgraduate students. It was not written for medical practitioners but it should be a valuable reference book for the experienced virologist. In order to satisfy the latter group, it will have to be brought up to date frequently, since the rate of progress in this field is formidable.

Principles of Nutrition. By Eva D. Wilson, Professor of Foods and Nutrition, Katherine H. Fisher, Associate Professor of Foods and Nutrition, and Mary E. Fuqua, Associate Professor of Foods and Nutrition, all at Pennsylvania State University, University Park. Cloth. $5.95. Pp. 483, with illustrations. John Wiley & Sons, Inc., 440 Fourth Ave., New York 16; Chapman & Hall, Ltd., 37-39 Essex St., Strand, London, W. C. 2, England, 1959.

For the student just being introduced to the study of nutrition, an up-to-date readable textbook is a real boon. The authors of this excellent book have done an admirable job in presenting basic nutritional information in a way that does not depend on a background of chemistry and physiology. The first chapter defines nutrition as the science of nourishing the body; the second chapter discusses the basic terms that one should know for the study of nutrition. This enables the student without a background in science to embark on his course of study without being unduly penalized for his vocabulary deficiency.

The first part of the book discusses the principles of nutrition, including information on energy, metabolism, and nutrients; emphasis is placed on the needs of the college student. The remainder of the book shows how these concepts apply to the requirements of children, pregnant and lactating women, and older persons. Problems concerned with nutrition as related to obesity, dental health, and other special considerations are taken up in the last section.

The discussion of the treatment of obesity and food fads and fallacies is timely and well presented. The roles of the Food and Drug Administration and the various other groups concerned with accurate nutritional information are stressed. An entire chapter tells the student how to select an adequate diet. This book should appeal not only to the student but also to the nutritionist, dietitian, and homemaker. The physician desiring a concise, comprehensive source of nutritional information would do well to add this volume to his library.

The Mediastinum. By Ted F. Leigh, M.D., Professor of Radiology, Emory University School of Medicine, Emory University, Georgia, and H. Stephen Weens, M.D., Professor of Radiology and Chairman of Department of Radiology, Emory University School of Medicine. Cloth. $11.50. Pp. 246, with 290 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

The mediastinum, though a small anatomic compartment, contains more vital structures than any other compartment in the body. Practically every organ system is included in this area. The lesions that arise from these systems are many, yet they may so closely resemble each other that they almost defy differentiation. The lesions are similar as they produce the same symptoms and have similar roentgenographic features. An attempt to separate these lesions by their symptoms would prove discouraging. The best approach is by their roentgenographic appearance.

The authors first discuss the normal roentgenographic features of the mediastinum and its contents. From this point the various mediastinal tumors are dealt with according to the organ systems from which they arise. Only the diagnostic features are discussed and illustrated by numerous roentgenograms gathered from many sources. The lesions are not discussed from therapeutic or prognostic viewpoints. This is justifiable as the purpose of the work is the accurate differentiation of mediastinal lesions prior to exploration.

The authors have dealt with the subject thoroughly and concisely and have included many excellent illustrations. The book is highly recommended to those who are confronted with the problem of accurate diagnosis and treatment of mediastinal diseases.

Physiology of the Eye: Clinical Application. By Francis Heed Adler, M.A., M.D., F.A.C.S., William F. Norris and George E. de Schweinitz, Professor of Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia. Third edition. Cloth. $16. Pp. 790, with 372 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3; Henry Kimpton, 134 Great Portland St., London, W. 1, England, 1959.

Students of ophthalmology are fortunate that this book has appeared in a new enlarged edition. The general plan and chapter headings remain the same as in earlier editions. The excellent bibliographies that follow each chapter have been brought up to date and constitute a valuable feature of the book. There have been extensive additions to those chapters dealing with subjects in which there has been much investigative work in the past six years. This particularly applies to the chapters on aqueous humor, intraocular pressure, and ocular motility. The author has the faculty of expressing himself clearly and succinctly so that even the most complicated matters appear simple. The format of the book is pleasing and the illustrations are good. This book should be required reading for all students of ophthalmology, clinicians, investigators, and residents.

Lectures on the Interpretation of Pain in Orthopedic Practice. By Arthur Steindler, M.D., F.R.C.S., F.R.S.M. With anatomical dissections by Dr. Rodolfo Cosentino. Cloth. $18.50. Pp. 733, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

The author believes that there are two concepts against which the student should be thoroughly immunized. The first is the idea that one must be dealing with a psychoneurosis if the origin of a pain cannot be established. The other is the defeatist viewpoint expressed by telling the patient that he will just have to live with his pain. The physician should determine whether a certain painful syndrome is of peripheral origin, such as that caused by the pressure of a herniated nucleus pulposus on a nerve root, or if is of central origin and within the domain of the neurologist and neurosurgeon. Pain speaks its own language. If pain is premonitory of a presenting sign, a careful analysis may reveal the condition while it is still in a reversible stage.

The broad coverage of this subject is indicated by the following list of subjects discussed: the perception, conduction, allocation, and appreciation of somatic pain; interpretation of pain; evaluation of pain and the clinical analysis of pain syndromes; the autonomic nervous system in the pain syndromes of orthopedic conditions; joint pain; pain in muscles, tendons, and fasciae; bone pain; neuralgia; causalgia, and phantom pain; central pain and orthopedics; the cervical pain syndrome; the pain syndromes of the thoracic spine; lumbosacralgia and sciatica; the shoulder pain syndrome; the shoulder-hand syndrome; pain syndromes of the elbow and forearm; pain syndromes of the hand and fingers; the pain syndrome in disturbances of the hip and knee joint; and pain syndromes of the foot, ankle, and leg. Most of the illustrations are instructive.

The orthopedist is confronted with three principal complaints: deformity, dysfunction, and pain. Pain has become a stepchild of orthopedic investigation compared to deformity and dysfunction, on which much energy is expended. Every type of orthopedic situation is analyzed here from the standpoint of pain syndromes for the purpose of diagnosis and therapeutic indications. The analysis of pain is presented as a special feature in diagnosis and therapeutic indications. The author is to be commended for so ably bringing this subject to the attention of the profession.

QUESTIONS AND ANSWERS

ERYTHEMA NODOSUM

To the Editor:—*What percentage of patients with erythema nodosum also have enlarged hilar lymph nodes? What is the cellular appearance of the enlarged nodes when examined microscopically? Has any relationship between erythema nodosum, hilar adenopathy, and sarcoidosis been established?*

Martin A. Thomas, M.D., Tampa, Fla.

Answer.—Erythema nodosum may occur in patients concurrently with or after they have had many diseases, including upper respiratory infections, tuberculosis, leprosy, sarcoidosis, various pulmonary disorders, infections with beta hemolytic streptococci, peritonsillar, prostatic, or axillary abscesses, appendicitis, eye infections, dental infections, brucellosis, meningococcemia, the communicable diseases, influenza, herpes zoster, coccidioidomycosis, venereal diseases, ulcerative colitis, regional ileitis, and Hodgkin's disease and other neoplasms, or after drug ingestion. Erythema nodosum is considered to be a hypersensitivity reaction to a variety of infectious agents, drugs, and other allergens.

Regardless of the etiological factors involved, enlarged hilar lymph nodes with or without pulmonary changes occur in about 9 to 10% of patients with erythema nodosum. In selected series the incidence of hilar adenopathy has been reported as from 2 to 95%.

When adenopathy is due to a primary disease such as tuberculosis, sarcoidosis, Hodgkin's disease, or coccidioidomycosis, the microscopic appearance is usually specific for that disease. When adenopathy is the result of a streptococcic infection, a drug reaction, or some other hypersensitivity reaction, it presents the appearance of nonspecific adenitis.

Erythema nodosum occasionally occurs in a patient with sarcoidosis, but determination of the incidence is confusing because the appearance of the chest roentgenogram in the two conditions may be identical and the clinical appearance of the skin lesions indistinguishable. Microscopic study of the early skin lesions of erythema nodosum shows them to be infiltrated with neutrophils, lymphocytes, occasional histiocytes, and eosinophils, and in some specimens severe vasculitis is present. In the late stage of the disease, small nodules with epithelioid cells in a radial or palisaded pattern and foreign body giant cells also may be present. Since the erythema nodosum lesions can be confused with those due to sarcoidosis, differentiation of the two conditions must be made on the basis of the full clinical picture exhibited by the patient as well as the results of pathological studies.

DIFFERENTIAL WHITE BLOOD CELL COUNTS

To the Editor:—*The results obtained from the differential blood cell counts performed on the medical patients admitted to our hospital have shown less than 1% monocytes and eosinophils (average obtained from groups of 10 to 40 patients). Most of the reports of blood cell counts do not list either of these cells as present. The physician director of the laboratory insists that these monocyte and eosinophil counts are not necessarily in error and that the variation from "normal" is due either to the patient's illness or to the medicaments he is taking. Is this explanation valid?*

M.D., Michigan.

Answer.—Failure to record the presence of either eosinophils or monocytes in the routine admission differential blood cell counts of a majority of patients suggests some error in the technique of staining or of counting, or a variation in the interpretation of cell type. In my experience, less than 20% of initial differential counts fail to show 1% or more of either eosinophils or monocytes in a count of 100 cells.

The eosin-staining quality of the stain being used may vary with the batches of stain and with differences of staining technique, so that the eosinophilic coloring of the cell may not be evident. Variation in staining quality or technique usually does not influence the appearance of the monocyte; hence *the failure to record the presence of monocytes is* more likely to be due to differences in interpretation of the cell type by the persons who are doing the counts. Monocytes can be recorded as metamyelocytes, a recent trend in some laboratories, or they may be recorded as large lymphocytes. Since an accurate differential blood cell count must enumerate 100 different cells, it is important to avoid repetitive scanning of the same area of the smear. A *microscope-slide carrier*, which may be moved accurately from side to side and up and down, is useful for this purpose.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

No drug commonly administered to patients prior to their admission to a hospital would alter the number of eosinophils or monocytes in the stained blood smear.

FINGER DERMATOSIS OF UNKNOWN CAUSE

To the Editor:—*A 50-year-old patient has had a dermatosis of the palmar surface of the fingers, confined to the distal half of the phalanges, for two years. The lesions first appeared as brownish spots less than 0.5 mm. in diameter. Later, the skin overlying the spots cracked, desquamation occurred, and on examination small excavations filled with a serous fluid were found. What are the diagnostic possibilities?*

M.D., New York.

Answer.—Cultures of the vesicular fluid, grown on both regular agar for bacteria and on Sabouraud's agar for fungous infections, are mandatory for this inadequately described condition. The possibility of contact dermatitis must be considered, and, if necessary, the patient should have a patch test for industrial allergenic materials.

The vesicles could also be an "-id" reaction caused by a focus of infection in the tonsils, ears, prostate gland, or other organs.

EUGENIC COUNSEL IN ALZHEIMER-PICK SYNDROME

To the Editor:—*A 47-year-old woman has presenile sclerosis (Alzheimer's disease). Her father received continuous institutional care for mental deterioration for eight years prior to his death at the age of 50 years. The patient's husband would like to know whether their two sons should marry and have children. What advice can I give him?*

Stephen B. Yohalem, M.D., New York.

Answer.—Giving eugenic counsel to a family afflicted by a condition such as the Alzheimer-Pick syndrome is extremely difficult, since the mode of inheritance is not yet defined and specific advice about the probability of affected offspring cannot be given with any degree of statistical significance. Another complication is that the differential diagnosis between Alzheimer's and Pick's disease usually cannot be definitively confirmed without performance of a histopathological examination of the brain tissue.

The best genetic description of the Alzheimer-Pick syndrome has been done by Sjogren and coworkers (*Acta psychiat. et neurol. scandinav.* [supp. 82] 1952). While in Alzheimer's disease the morbidity risk for the parents of probands appears to be about 10±4% and for the siblings of probands about 3.8± 2.1%, the corresponding figures for Pick's disease are 19± 5% and 6.8± 2.9% respectively. The mode of inheritance in Alzheimer's disease appears to be multifactorial (a polygenetic disturbance with cumulative action of genes), and the picture is possibly complicated even more by some environmental factors. Pick's disease is thought to be due to an autosomal dominant gene and other modifying genes. Eugenic counsel would consist of an explanation of the factual information about the disease to the family. No suggested course of action can be outlined.

CYANOSIS DECREASED BY CRYING

To the Editor:—*What causes a baby to have a cyanosis that becomes less severe when it cries?*

M.D., South Carolina.

Answer.—To answer the question with accuracy, more information, such as the infant's age, nutritional status, respiratory rate, characteristics of its cry, and whether a cardiac murmur is present, is necessary. Asphyxia is characterized by cyanosis which decreases with crying and in children often is caused by atelectasis. Other causes of asphyxia, such as increased intracranial pressure, should be investigated. The infant may also have persistent atrioventricularis communis, which is a congenital malformation of the heart.

ATOPIC ECZEMA AND VACCINATION

To the Editor:—*With reference to the item, appearing in the Questions and Answers section of* The Journal, *June 27, 1959, page 1137, "Atopic Eczema and Vaccination," although a smallpox vaccination within three years is required for persons entering the United States, consideration will be given to a physician's statement that vaccination is medically contraindicated. The person should present the statement to the quarantine officer at the time of arrival. That officer will determine what procedures are applicable to the individual case, depending on the possibility of exposure to smallpox. The person may be placed under surveillance (reporting to the health officer at the point of destination) or in isolation. The period of surveillance or isolation is 14 days from the date of the last possible exposure to smallpox. The decision will be based on the presence or absence of smallpox in areas visited or contacts en route during the same period. As a basis for the above judgment, the foreign quarantine officers at United States ports of entry are kept currently informed on the occurrence of smallpox throughout the world. Complete information concerning the requirements for entrance into the United States is given in section 4 of the U. S. Public Health Service booklet "Immunization Information for International Travel."*

Andrew P. Sackett
Department of Health,
Education, and Welfare
Washington 25, D. C.

WASHINGTON NEWS

Social Security Hearings . .
Medicare Costs Increase . .
Drug Hearings Criticized . .
Tighter Labeling Law . .
International Research Bill . .

COMMITTEE OPENS SESSIONS ON SOCIAL SECURITY CHANGES

The House Ways and Means Committee launched crucial hearings on proposed amendments to the social security program. The controversial Forand proposal was one of the items on the agenda.

First witness at the closed-door sessions was Arthur S. Flemming, Secretary of Health, Education, and Welfare. He was reported to have told the Committee members that he was not prepared then to discuss the administration's stand on important social security changes, because this was still under study by the administration.

Flemming was asked to come back at a later date with the administration's recommendations. The HEW Secretary has indicated repeatedly that the administration would offer some type of alternate to the Forand proposal this year, but there was no certainty, as the hearings opened, whether this would be done or what form it might take.

The proposal would broaden social security to include financing of partial health care of the elderly through higher taxes. Rep. Aime Forand (D., R. I.), sponsor of the legislation that is opposed by most business and health organizations as the first step toward complete government control of medicine, said that if the Committee failed to act on the measure he might resort to the seldom-used discharge petition to bypass the Committee and bring the bill up for a vote by the full House.

Meanwhile, the American Farm Bureau Federation wrote the members of the influential ways and means group urging them to turn down the Forand proposal. Enactment "will lead to the socialization of medical and hospital care," said the organization. "This legislation is based on the false assumption that most aged persons cannot finance their own health care needs."

MEDICARE EXPANSION SEEN

The Defense Department's Medicare program, which provides medical care in civilian and military hospitals for qualified dependents of military personnel, will cost more in the future "as the military dependent population grows."

Gen. Floyd L. Wergeland, executive director of the Medicare program, told Congress that the number of families eligible for Medicare will rise to about 3,700,000 in the fiscal year starting July 1, an increase of 200,000 since 1959.

Cost of the program next fiscal year will be about $71,600,000, he told the Senate military appropriations subcommittee, about $2,100,000 above the current fiscal year's cost.

Care for service families in both military and civilian hospitals will rise by about 550 patients a day in fiscal 1961, with the average daily load in civilian installations increasing to 3,200. In military hospitals the daily family load will climb from 9,470 to more than 9,700.

The program, according to the witness, is "now sound and stabilized" and will "increasingly improve the stamina and morale of servicemen."

General Wergeland also said that "a permanent control feature of the program" will be the current permit system under which civilian dependents residing away from their sponsors are required to have permits stating that care in military medical facilities is unavailable as a provision for admission into civilian facilities.

The biggest user of Medicare is the Air Force, accounting for 40% of the cost. The Navy and Marines follow with about 32% and the Army with 24%. The remainder is accounted for by the Coast Guard, the Public Health Service, and the Coast and Geodetic Survey.

Other figures given the subcommittee by General Wergeland included:

Cost per patient per day in civilian hospitals averaged $52.65 this year and will rise to $55.60 next fiscal year. Last year the figure was $50.06.

Of the total $212,600,000 spent on the program since December, 1956, 49.3% represented physicians' claims, 48.5% hospital claims, and 2.2% administrative costs.

Referring to retention of the permit plan, General Wergeland said, "Of prime importance is the fact that the Medicare permit system is operating very effectively to channel patients into service hospitals and it does reduce substantially the cost of the civilian portion of the program."

DRUG HEARINGS SCORED

The dean of Temple University's school of pharmacy charged that Senate investigators were distorting the facts in their inquiry into drug companies' pricing practices.

Dean Joseph B. Sprowls, in a letter to Senate minority leader Everett Dirksen (R., Ill.), said, "If we are to have legislation which prevents the making of honest profits on the manufacture and sale of drugs, then our country and our government have certainly reached their declining years."

The only alternative, he said, is "total socialism—government-directed medical practice and research."

Noting criticism of the drug industry by Sen. Estes Kefauver (D., Tenn.), chairman of the Senate antitrust subcommittee that is currently investigating drug companies, Sprowls said, "Attempts to demonstrate excessive profits by the use of calculations involving only the basic cost of ingredients and the ultimate selling price of finished products are . . . gross misrepresentations of the truth."

Medical and drug research owe their stimulus to the "highest of humanitarian ideals—the desire to relieve suffering and to save lives," he said. "On the other hand, the motive which stimulates the investment needed to make such research possible is the profit motive."

Sprowls said proposals by Kefauver for tighter federal supervision of some industry practices would seriously curtail research efforts and impair the discovery and development of new drugs. "Let us hope that an enlightened electorate will never permit this to happen," he said.

In a speech on the Senate floor, Senator Dirksen, a member of the subcommittee, also attacked the investigation. He said "misleading and unfair exhibits" had "crept into" the hearings and noted various newspaper editorials supporting his charges.

A. M. A. URGES BROADER LABELING BILL

The American Medical Association asked a House commerce subcommittee to strengthen a bill for labeling hazardous substances in order to provide broader safety coverage and clearer warning symbols.

Dr. O. Benwood Hunter Jr., a Washington, D. C., pathologist speaking for the American Medical Association, told the subcommittee that while the need for appropriate labeling of household substances has been amply demonstrated, there is also need for such protection for those engaged in nonmanufacturing occupations.

Neither the bill before the House group nor one that has been approved by a Senate Commerce committee would cover the latter category.

Noting that manufacturing concerns such as large chemical plants "are among the safest places to work because of enforced safety rules." Dr. Hunter pointed out that this does not apply to two-thirds of business enterprises, which are either retail trade establishments, such as grocery stores and filling stations, or service establishments, such as hotels and laundries.

"These firms employ a major portion of the labor force and provide the least organized medium for maintaining the workers' safety," said Dr. Hunter.

"While no information is available as to the number of injuries associated with unlabeled or poorly labeled chemical products, our concern is based on the belief that warning statements of the hazardous ingredients are needed just as much by workers who do not have the benefit of safety programs as they are in the home."

Dr. Hunter also recommended that the bill be changed to include such symbols as the skull and crossbones to emphasize the danger in addition to words as "danger," "caution," and "warning."

At present there is no national law requiring the precautionary labeling of hazardous substances, other than those used in foods or drugs or caustic poisons. The legislation in Congress was modeled to a large extent on the recommendations of the A. M. A.'s Committee on Toxicology. Accompanying Dr. Hunter at the subcommittee session were Bernard E. Conley, Ph.D., Secretary of the Committee on Toxicology, and Paul R. M. Donelan, A. M. A. Legislative Attorney.

SCALED-DOWN INTERNATIONAL MEDICAL RESEARCH BILL APPROVED

A House commerce subcommittee unanimously approved a measure authorizing 10 million dollars for a program of international medical research cooperation. Under the legislation, an office to carry out the program would be established in the Department of Health, Education, and Welfare. The widest possible use should be made of foreign currencies derived from the sale of U. S. food surpluses for international medical studies, said the subcommittee.

The Senate last year approved a broader bill authorizing a 50-million-dollar appropriation and creating a separate Institute of Health to administer the program. The administration opposed the measure on grounds it was not necessary and that instead existing programs should be strengthened. The American Medical Association has endorsed the principle of the legislation but proposed that final action be held off until an over-all assessment can be made of various proposals before Congress dealing with domestic and international research.

Commenting on the subcommittee bill, HEW Secretary Arthur S. Flemming said, "I am glad to note that the subcommittee has moved in the direction of the recommendations we made."

The bill is sponsored by subcommittee chairman Kenneth Roberts (D., Ala.).

MISCELLANY

The U. S. Court of Appeals in New York upheld a lower court decision compelling commercial airline pilots to retire from the cockpit at the age of 60 years. The decision came on a protest by the Air Line Pilots' Association against a Federal Aviation Agency order that pilots of commercial passenger planes could not be more than 60 years old. The ALPA said the order was arbitrary and threatened to carry the fight to the Supreme Court and Congress. Meanwhile, about 40 pilots over 60 years of age were forced to quit commercial flying.

"Mongolism—Hope Through Research," a booklet published by the Public Health Service, tells of research efforts at the National Institutes of Health to find the cause and prevention of the disorder. A new finding suggests that mongolism could begin with an irregularity in the human egg before it is fertilized.

The Federal Trade Commission charged that advertisements for a book entitled "How to Live 365 Days a Year" misrepresented that the method set forth in the book would effectively treat asthma, arthritis, cancer, heart trouble, and other ailments. The publishers of the book, written by Dr. John A. Schindler, agreed to discontinue the claims.

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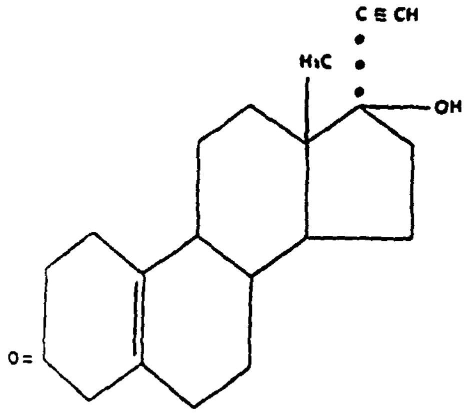

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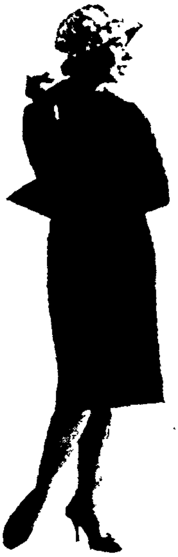

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PSYCHOTHERAPY

Kenneth E. Appel, M.D., Philadelphia

Physicians and surgeons in the future will be called on to do more psychotherapy than ever. Various methods of psychotherapy are available to the general practitioner: ventilation psychotherapy in repeated, unhurried interviews; supportive psychotherapy based on facts of physical examination and implemented by physiotherapy and hydrotherapy; manipulative psychotherapy, including occupational and recreational guidance; explanatory psychotherapy; and dynamic growth therapy. The case history of a patient with recurrent asthma and eczema illustrates the need for establishing basic human contact with patients. In many cases it is possible to achieve solid recovery without insight when enough time is allowed for the readjustment of the instinctive id and the social superego forces of the patient.

PSYCHOTHERAPY is widely misunderstood by many persons, including doctors and many psychiatrists. It is not a transfusion of ideas to the patient. It is not an injection of correct notions. It is not soothing him with platitudes, pacifying pronouncements, or phrases. It is not making decisions for the patient or solving problems for him. It is not manipulating a patient with a formula or prescription as one applies an orthopedic brace or gives iron therapy or an enema. It is not giving insight. It does not preclude the use of drugs; drugs may facilitate psychotherapy. It is a collaborative search for better adjustment to rectify a seriously disturbed emotional or conditioned state. It is either a search for a better resolution of frustrations, disappointments, resentments, depression, fears, guilts, distrust, insecurities, and resulting overdependency or compensatory overconfidence, or it may be guidance in meeting disturbances caused by multiple or long-continued stresses due to work situations, physical illness, or social pressures. It is helping the patient develop solutions, capacities, confidence, and respect through discussion, guidance, talking things out, and the release of pent-up feelings. It is a collaborative, searching, prospecting adventure from which confidence, resourcefulness, and help develop. Santayana has really described it, in his essay on Faust, as a drama of search, acceptance or forgiveness, and healing. Dostoevski has much to say about these functions.

Psychotherapy is a deceptive word, used glibly by physicians and laymen alike as if it were a simple process, well understood and easily applied. It is ancient but enigmatic, involving both science and art, fact and fiction, whose nature is often violently disputed by many. When one speaks of it as art, one implies that there is something intuitive and emotional about it—not unlike the feelings and resolutions that come at the end of great esthetic experiences. A resolution of feelings and new dedications take place, so that one is on a new plane or new road of living, with new purposes, resolutions, strengths, and directions. Successful psychotherapy,

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Professor and Chairman, Department of Psychiatry, University of Pennsylvania, School of Medicine.

Chairman's address, read before the Section on Nervous and Mental Diseases at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

it appears to me, is of a similar nature, in addition to its ideological, intellectual, and formally psychodynamic aspects. Neglect of the nonintellectual esthetic aspect often accounts, it seems, for many of the failures of psychotherapy.

Physicians and surgeons will be called on to do more psychotherapy than ever, since the introduction of the new tension-reducing drugs. Psychiatrists, who number only between 4 and 5% of the physicians of the United States, can never do the complete psychiatric job. Mental and emotional health is the job not only of the community but especially of the physicians who see patients in their homes and at the inception of illness. It is important that medical schools recognize these facts and afford instruction and training in the basic principles of psychotherapy.

The goal of psychotherapy is the development or restoration of mental or emotional health. Some of the characteristics of mental health may be listed, as follows: reasonable independence; self-reliance; self-direction; ability to do a job; ability to take responsibility; reliability; ability to make needed efforts; persistence; ability to get along with others; cooperation; accommodation—ability to work with others; ability to work under authority, rules, and difficulties; ability to show friendliness and love; ability to give and take; tolerance of others and of frustrations, tensions, and unpleasantness; ability to accept difference; ability to contribute; a sense of humor; devotion beyond oneself; and ability to find recreation, as in hobbies. Tolstoi expressed the goals of life as what men live by: love, play, work, and worship.

Causes of Emotional Illness

A few remarks about etiology and psychopathology may be helpful. Freud in Vienna and Adolph Meyer at Johns Hopkins University looked on most neuroses and psychoses as developmental processes rather than products of heredity and constitution, although these latter elements were not eliminated. These conditions they thought of as reactions to persons and circumstances during growth, developing predisposing tendencies or habits. The normal process of growth produces effectiveness, ability to solve problems, satisfactions, and health. Growth is an expanding, outgoing, and organizing series of processes or manifestations of the organism. Freud used the words libido, sex, and love to mean much of what I mean by the word growth. There is something creative about this.

Various interferences or blocks in the normal processes of growth, or blocks in personal effectiveness, goals, or ideals, produce fear, anxiety, anger, hostility, guilt, ineffectiveness, suffering, and illness. The interferences may be many: unusual runs of illness, misfortune, catastrophe (financial or personal) or death; or they may be blocks, due to disturbed human relationships, which result in feelings of frustration, neglect, rejection, domination, or overdependency, or factors of constitution or heredity. One sees here many factors entering into the formation of habits, inclinations, predispositions, aversions, temperament, and expectations. One's expectations are, whether conscious or unconscious, tremendously important in the development of health or illness. One sees here reasonable doubts as to the amount of responsibility one can attribute to an individual person and some of the reasons why logic and will power have their limitations in dealing with strong, prerational forces and dispositions.

Anxiety develops in response to excessive hostility, aggression, or eroticism. Anxiety is buffered by the various defense mechanisms: repression, dissociation, rationalization, extroversion, introversion-introjection, projection, conversion, reaction-formation (rituals), identification with the aggressor, and regression. Intense expressions of these defense mechanisms appear in illness—the manic overactivity of extroversion, the depression of introversion, the suspiciousness of projection, the physiological disturbances of the conversion of emotional tensions into bodily reactions, the antithetic reactions of the meticulous, obsessive perfectionist, and the regression of the extreme schizophrenic.

Psychiatry deals with personal and social stresses, whether in the past or in the present, the past being predisposing and the present being precipitating. Experience—handicapping, frustrating, or disturbing—is the source of ineffective direction of energies and the associated feelings of frustration, disappointment, and depression. Personal, social, and emotional experiences are causally related, in the present state of knowledge, more often than are such things as infection, trauma, toxic agents, deterioration, or tumor. The stresses of experience can be injurious (castrating) in a predisposing or in a precipitating way. Psychotherapy is counteracting or corrective experience. It is experience and practice, prospecting and searching, not just discussion, exhortation, reasoning, or handing over correct ideas to the patient. If handicapping, or traumatic, experiences have made a person oversensitive to people and situations and predisposed to emotional illness, psychotherapy must provide a healing experience. The effects of destructive experience can be changed only by a new and constructive experience such as psychotherapy can provide.

Psychotherapy is experience. It is broader than the verbal, intellectual, rational, ideal level of the personality. Infants have personalities, with strong emphases, predilections, and aversions, long before the intellect is much developed. They cannot be appealed to by reason, but they can be won or maneuvered by appropriate operations and procedures and so can patients with neuroses and psychoses. They are moved by subrational forces and systems. Reason and will power are often limited or impotent before the great surge of prerational forces. This does not mean that we cannot learn to understand these subrational systems and help them become more effectively modified and integrated into effective and mature systems of organization, action, and feeling.

Psychotherapeutic Methods

Various methods of psychotherapy, as summarized by H. Yaskin, are available to the general practitioner: 1. Aeration or ventilation psychotherapy begins with history-taking and continues by means of repeated, unhurried interviews in which the patient is given the opportunities for "confession" and discussion of his life history. 2. Supportive psychotherapy may start with the physical examination and judicious reassurance, establishing rapport and the opportunity for healthy identifications. Suggestions and the giving of illuminating information may follow, and therapy may include medical and physical treatment, including physiotherapy and hydrotherapy. 3. Manipulative psychotherapy may consist in occupational therapy, the development of hobbies, establishment of a daily routine, including diversion and entertainment, and vocational guidance, by these means producing a change in the patient's environmental attitudes. 4. Explanatory psychotherapy includes desensitization, persuasion, and reeducation by means of suggestion, direct or implied. 5. Finally there is a method which I term dynamic growth therapy, described in this paper.

Psychoanalysis is reserved, as are some other methods, for the specialists. However, psychoanalytic theories and practice have great influence on standard psychotherapy today. All methods can be used appropriately at different times in treating the same patient or different patients. A multifactorial approach is more often than not indicated—often including the use of drugs. Experience enables one to select a number of these procedures that seem possible and helpful at a given time. There are dangers in authoritarian direction, except in the severest conditions; it may arouse antagonism, uncooperativeness, or unwholesome dependency. Suggestions of alternatives for decision and action for the patient to select may stimulate the patient's initiative, resourcefulness, and independence, but many suggestions contain the danger of contrary-to-fact assertions on the part of the physician and work toward his diminished effectiveness or downfall in serious conditions.

Psychoanalysis

Psychoanalysis has been largely incorporated into general psychiatry. Among the psychoanalytic concepts now recognized are those of the unconscious, repression-resistance, dissociation, defense mechanism, transference, abreaction, analysis, and insight. In fact, except for the use of the couch, the depth of analysis, the emphasis on the Oedipus and castration complexes, and the interpretation of dreams, fantasies, and infantile impulses, general psychiatry borrows greatly from psychoanalysis. The principles of psychoanalytic therapy, and the various aspects of it, may be summarized as follows.

The relationship with the therapist is of basic importance; it may be at various times one of confidence, support, submission, distrust, antagonism, marked dependence, or independence. The patient's feelings often are intense, exaggerated, distorted, or inappropriate. The concept of abreaction means the ventilation or free expression of feelings. Transference is a process of displacement, often inappropriately, of feelings from an important person in the past to the analyst. Other techniques include free association, with subsequent intellectual analysis, and interpretation of dreams, fantasies, symptoms, displacements, and resistances.

Free association, analysis, and the interpretation of dreams and fantasies are not employed in psychotherapy with anything like the detail and consistency that they are in psychoanalysis. A definition of psychotherapy that has been useful is the following one: helping people handle their feelings, motivations, and behavior more effectively. This indicates the broad nature of psychotherapy and also indicates that it is not limited to words, planned rational discussions, reasoning, or argument. People can often influence others more effectively by what they do, their manner, and their attitude than by what they say. What is left unsaid is sometimes more important in human relations and in treating emotionally sick patients than what is said. It is a great art to know when not to voice the truth. Dr. Samuel Crothers said that the ability to know what people do not want to hear about themselves and not to say it is a good definition of tact.

Report of an Illustrative Case

A patient in her early 20's had been ill for most of her life with eczema and asthma. She had had treatment both in the United States and abroad in many clinics. Many forms of drug therapy and chemical treatment had been used. She was becoming increasingly depressed. Injections of allergens did not help. It seemed to me that, essentially, her problem was one of lack of security, dating from an early age. She came from a home in which there was an asocial alcoholic mother and an alcoholic father who committed suicide. In the several years before I saw her she had had such severe attacks of asthma that the internist thought she might die. Along with these attacks came terrific outbreaks of eczema. It seemed to me that this young woman needed security. She received treatment with mild doses of sedatives during the day and hypnotics at night. The chief concern was to see her, be with her, and give her all the security possible. This was done, whether for five minutes a day or a half-hour or hour. Some days, of course, she was not seen. Everything that was on her mind was talked about. She discussed what she read, what movies she had seen in the past, and how she felt about friends and relatives. An effort was made to build a solid, secure relationship with her. Sometimes she sat like a frightened animal underneath the table in her hospital room. I frequently sat on the floor beside the table and talked to her. It seemed essential to establish basic human contact with this patient. She got well, and I think I had something to do with her recovery. I do not think that without some kind of rational treatment based on understanding her personality, her experiences, and her needs she would have become well. She had shown no improvement for 20 years. She married and has been well for seven years, living in one of the most competitive cities of the United States. This therapy was social, psychological, and emotional therapy. Her cure was not the result of drugs or chemicals or the result of geographical change. Her cure, it seemed to me, was the result of the establishment of a secure understanding relationship with her therapist—helping her develop a workable amount of security.

Psychotherapy here was not explaining to her how she became ill or making clear to her the linear sequences of her personality development, although the search for clarification is always important. An understanding of the personality development of the patient and the dynamics of the illness on the part of the therapist is much more helpful than it is on the part of the patient. It was not reasoning or explaining how she became ill or the psychology of rejection and insecurity, hostility and guilt; it was not a discussion of psychosomatic medicine or the influence of the emotions on the body. It was providing a setting for her, an opportunity for growth, a search for effectiveness and the acquisition of security. She had new experiences to which she was conditioned, much as the dogs of Pavlov were conditioned. This experience was not just intellectual, it was social and emotional. There was much release of feeling or abreaction. Much of this kind of therapy goes on without the patient's awareness. It is automatic and unconscious. An unconscious readjustment of the forces of the personality takes place. The automatic readjustment does not take place merely as the result of intellectual understanding and reasoning. This patient made a solid recovery, as do many patients, without insight. A readjustment of the instinctive and the moral superego forces of the patient takes place so that the intellectual and ego, or executive, forces of the psyche can take over. Psychotherapy is thus a process of conditioning and reconditioning. It takes time and cannot be done, in severe conditions, by brief exhortations and reasoning.

A factor of great importance in psychotherapy is identification. The patient gradually sees the physician tackling difficult problems and proceeding in certain ways. The doctor asks himself, "What are the things to do, what are the possibilities, what has contributed to this?" Through questions the physician establishes a certain amount of identification with the patient. He moves beyond the patient's immediate problems and says, "There is probably something that we can do with this." No situation is so terrible that something constructive cannot be done. The patient gradually takes over. This is an automatic process of identification with the physician and the role he performs.

The Structure of the Personality

The structure of the personality in its three elements, the intellectual perceptive ego, the instinctive id, and the social superego, may be summarized as follows. The conflict often is between the id and the superego. The ego is the rational component, whose functions include perception, classification, correlation, the search for truth, reasoning, planning, and problem-solving. The id is the emotional component, containing forces arising from body chemistry and metabolism. It is the reservoir of psychic energy of the emotions and impulses, love (the impulse to be with), fear (the impulse to be away), and hate (the impulse against). Love has many expressions, including *élan*, eros, libido, growth, curiosity, multiplicity of interest, productivity, and creativity.

The superego is the social component, providing motivations for attraction (liking) and aversion (disliking), identification (transference), opposition (reversal), expectations, and aspirations, and containing the basic elements of the person's standards, values, and concept of duty. Basic needs of the whole personality include those for security, affection, "belonging," individuality, difference, respect, understanding, and change.

The patient with asthma had persistent insecurity, stemming from her fear of her mother and father, which was transferred to people in general. When the lack of trust in people became intense she had her asthmatic attacks. The therapeutic beginning was to find someone with whom she could find security and confidence. When this was established with the therapist and hospital personnel, it spread to other relationships and the violent autonomic responses subsided and disappeared. She was not aware of these mechanisms. This is what is meant by unconscious therapy, which can take place without insight. One of the most important aspects of therapy is for the physician to tap the constructive forces in the eros, *élan*, or growth impulses of the patient. Psychotherapy should search for and mobilize the interests, assets, and resources of the patient, as well as consider inadequacies and mistakes. This approach enables the patient to expand, take initiative, and develop constructively. Patience, consideration, understanding, and hope are great therapeutic forces.

The words of a great physician can yet guide the psychiatrist: "The good physician knows his patients through and through, and his knowledge is bought dearly. Time, sympathy, and understanding must be lavishly dispensed, but the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, where the secret of the care of the patient is in caring for the patient."

111 N. 49th St.

THE PSYCHOTHERAPY OF PARALYSIS AGITANS

Lewis J. Doshay, M.D., Ph.D., New York

Patients with paralysis agitans need the help provided by antiparkinsonian drugs, by new tranquilizers, antihistamines, muscle relaxants, and cerebral stimulants, and by physical therapy. But it is the psychotherapeutic approach of the physician that binds the entire treatment together. Patients in the early, ambulatory stages of the disease afford favorable prospects for long-term care by the family physician. It is important to maintain their confidence and cooperation and to keep them optimistic and active, since research in this field is progressing and promises increasingly effective remedies.

Probably in no other branch of medicine is psychotherapy as important or effective as in paralysis agitans (Parkinson's disease). It is the psychotherapeutic approach of the physician that serves to bind the entire treatment together. Without it the patient loses confidence in his medicaments, discontinues visits to the physiotherapist and doctor, and deteriorates in a relatively short span of time. The writing of this paper was prompted by the fact that little attention has been given this subject in the literature. There has been an effort to point up what the psychiatrist can accomplish for patients with paralysis agitans by means of group psychotherapy.[1] However, no one has outlined a practical plan of everyday psychotherapy that would be useful to general practitioners in the treatment of 98% of their patients.

Why are these patients especially suitable for psychotherapy? Because, aside from symptoms caused by damage to the basal ganglions, the brain proper (cortex) and its pathways are not involved. These people have symptoms of rigidity, tremor, akinesia, and loss of automatic movement,[2] but they have good preservation of all mental faculties. They can be reasoned with and properly directed. True, ignorance with regard to the nature of the illness and fear of later invalidism may lead some of them to become unduly alarmed and depressed. However, under suitable orientation and reassurance, they generally manage to steer a stable course.

Patients with paralysis agitans are of fundamentally sound character. Sands[3] once described them as good citizens—hardworking, self-sacrificing, and devoted to the welfare and interests of others, especially the immediate family. They are people who have given a lifetime of service to their families and communities and hence are deserving of help in their hour of need. Clinical experience has shown that selfish people hardly ever develop paralysis agitans, habitual criminals almost never, and imbeciles and idiots never.

Nature of Psychotherapy

Every doctor can and often does employ psychotherapy, sometimes even without realizing it. It basically consists of four elements: (1) orientation of the patient as to the nature of his illness, (2) concern for the patient's symptoms and ailments, (3) lending a sympathetic ear to the patient's personal problems, and (4) reassurance of the patient and family during each visit.

From these elements it should be obvious that one does not have to be a trained psychoanalyst to provide effective psychotherapy to patients with paralysis agitans. Psychoanalysis is almost never required in such patients, since we are dealing with an organic ailment and patients are usually past the age of crises that arise from sexual cravings or frustrations. Similarly, hypnosis is of little or no value in patients with this illness, since even when used with maximum skill it affords but momentary benefits.

The general practitioner is fully equipped by training and experience to provide all the psychotherapy that is required by his patients if he takes the interest and time. In only about 2% of such cases does the occasion arise when he has to obtain the help of a qualified psychiatrist.

Orientation of Patient.—The patient can and should be fully prepared to understand the nature of his illness. He must not be left to rely on stray bits of information, or misinformation, from neighbors, friends, newspapers, or magazines. He should be advised that the chief symptoms are rigidity and tremor, which can be helped by current treatment if he cooperates faithfully with his doctor. Under such conditions, 86% of these patients can be maintained in a good state of vocational and functional usefulness for 10 or more years at work, in caring for home and children, or in self-care. Cooperation entails regular visits to the office or clinic once a month if possible.

Every patient must learn the following facts. Paralysis agitans is neither inherited nor contagious. Since the brain proper is spared in this illness, speech and mental faculties are not affected and there is no paralysis or numbness. The reasons for this should be explained clearly. Better medicaments are being discovered for the control of tremor. Rigidity is helped not only by medication but by physiotherapy and exercise. Tremor is rarely of

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From the Department of Neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute of Presbyterian Hospital.

serious consequence to the patient's health and welfare, except when it affects employment or in instances of major tremor.[4] There is no pain in this illness unless contractures develop, usually as the result of neglect. There are far worse ailments than paralysis agitans; examples are brain tumor, leukemia, and multiple sclerosis. For reasons as yet unclear, this disease tends to protect the patient against developing cancer, coronary disease, hypertension, tuberculosis, and certain other ailments that afflict mankind. Better drugs continue to be created by the pharmaceutical houses, and tomorrow, next month, or next year, we may have drugs that are 10 times better than any we have today. New procedures and tools in the field of brain surgery are being studied for relief of tremor and rigidity among patients who fail to respond to conservative treatment. Within the past three years, chemical substances have been discovered that can produce the symptoms of paralysis agitans in "normal" people. This unfolds the unprecedented possibility that other chemical substances may be found that will act as antidotes and prevent the symptoms, or arrest them after they have set in. Quite recently two research foundations have been established for the purpose of doing research on the cause and prevention of paralysis agitans, for discovering better treatment measures, and for creating better facilities for afflicted persons. The National Parkinson Foundation has just embarked on a basic research project at the biological science department of the University of Chicago, and the Parkinson's Disease Foundation has established the first brain bank in this country, geared to research in pathology of paralysis agitans. Other programs will no doubt soon get underway.

These and other points of orientation, with amplification and illustration where possible, should be presented to the patient and family in order to provide hope, confidence, and purpose to treatment. They also serve to cement a lasting and beneficial relationship with the doctor. In this illness, confidence of the patient is of paramount importance. For example, in an acute illness such as pneumonia, the entire aim of treatment is geared to the destruction of the infective process, with little, if any, regard to the patient's attitudes, personality, or confidence. It is different in cases of paralysis agitans, where we are not dealing with a germ but with a chronic degenerative illness in which treatment can prove totally useless without the confidence and cooperation of the patient.

Concern for Patient.—In order for the doctor to merit the continued cooperation of the patient, he must exercise true concern for his needs and welfare. The needs of the patient are to carry on successfully, despite his ailment, and to be protected against later disabilities to the maximum extent. To meet these needs, the doctor must keep abreast of the latest advances in medication and pay close attention to the three essentials of therapy.[5] To those so prepared, paralysis agitans disease affords highly favorable rewards, since it is actually one of the easiest ailments to treat.

The patients do not expect a cure and are appreciative of any betterment in their condition. Daily automatic acts, such as putting on a coat or getting out of bed, which to us have little meaning, may be of great moment to such a patient. When the patient's ability to get out of bed is restored, he is spared the aggravation of having to awaken his family five times a night in order to get him safely to the bathroom.

No complicated tests or hospital stays are required, as in other disease, in order to establish the diagnosis of paralysis agitans. Generally, a glance at the patient, with his fixed facies, absent swing in the arms, shuffling gait, slow movement, and tremor of a limb, suffices. The cogwheel rigidity of wrist, elbow, knee, or ankle and the monotone quality of speech add further confirmation.

We have a growing armamentarium of effective remedies. Among these are standard medicaments such as trihexyphenidyl (Artane) hydrochloride,[6] cycrimine (Pagitane) hydrochloride,[7] procyclidine hydrochloride (Kemadrin),[8] benztropine (Cogentin) methanesulfonate,[9] ethopropazine (Parsidol) hydrochloride,[10] orphenadrine (Disipal) hydrochloride,[11] and chlorphenoxamine (Phenoxene) hydrochloride.[12] In addition, the physician has at his disposal many other suitable and helpful preparations such as dextro amphetamine (Dexedrine) sulfate, diphenhydramine (Benadryl) hydrochloride, hyoscine hydrobromide, and a number of new tranquilizers, antihistamines, muscle relaxants, and cerebral stimulants. The references to these preparations are provided as source material for those not fully acquainted with the actions, dosage, and side-effects of some of the newer compounds. Occasions arise among hypersensitive patients, especially of the elderly type, when excess or even moderate dosage of a drug may lead to toxic reactions of confusion, delirium, and possibly visual and tactile hallucinations. These usually disappear within a day or two if use of the drug is discontinued. Similar symptoms, when produced by cerebrovascular disturbances in the aged, may take days or weeks to disappear, and there is a tendency toward recurrence of the episodes. In such events, the advice of a neurologist should be sought.

Medication is one of the essentials of therapy. Physiotherapy is another, and it should be strongly recommended to every patient suffering from rigidity. The patient must be made to realize not only its value but also the reason he must use it early and continuously, since once contractures develop to an irreversible degree it becomes useless.[13] Exercise by the patient is the third component of the three essentials of therapy, and it should be stressed both as a means of prevention of later contractures and as a means of correction of those already acquired. The doctor must also be reasonably well prepared to discuss with the patient and family the advantages and disadvantages of neurosurgery.[14]

Lending a Sympathetic Ear.—During the long course of the illness, the patient may be harrassed, not only by the symptoms but by endless complications that older people fall heir to—such as memory impairment, otosclerosis, vertigo, tinnitus, headaches, cardiac problems, mental depression, nervousness, fear of the future, insomnia, fatigue, weakness, loss of weight, constipation, urinary problems, swollen ankles, dental problems, and visual disorders. He may suddenly develop a hernia, hemorrhoids, an ulcer, gallbladder disease, or diabetes, or he may fall and fracture a leg. He may also be confronted by problems relating to his work, retirement, rest, exercise, diet, travel, and family difficulties. For such situations the patient requires frequent audiences with his doctor. Not all his problems are subject to successful solutions, but he needs a sympathetic ear in order to make it possible for him to carry on and hurdle his difficulties. No one is better equipped to comfort the patient than the family doctor, who knows his background, temperament, and failings and has repeatedly helped him in the past.

Reassurance to Patient and Family.—Every chronic illness that cripples the body but spares the mind is bound to bring about a certain amount of discouragement and depression, and paralysis agitans is no exception. Some people bear hardships with greater fortitude than others because of greater strength of personality or because background experiences have better prepared them to face life's reverses. Others have secure family members to fall back on for emotional and physical support, and, hence, can withstand their plight with greater equanimity than widows, for example, who live alone despite much suffering and privation because they do not wish to burden their children.

Generally, the mild and ambulatory patients have ample automatic and free activity of the trunk and uninvolved limbs and possess speech and all mental faculties; hence they continue to perform successfully their usual duties of home and shop. Such patients require but little reassurance because they are well equipped by emotional reserve, physical adequacy, and buoyancy of spirit to carry on for many years with a minimum of help from the doctor. They maintain a hopeful attitude that better things will come and are grateful that they are no worse than some patients they see about them.

They do not deviate into frank depressions unless the effects of medication wear off and there is a progression in the symptoms, as when they suddenly find they cannot get out of a chair without assistance. Fears of future invalidism enter, accompanied by alarm, anxiety, and apprehension, which can aggravate tremor, muscle spasm, and physical inadequacy. Other events that may suddenly set them back emotionally and physically include a death in the family, loss of weight, or a fall and injury. Since fears of this nature are usually groundless, the doctor can call into service the most appropriate items listed previously. They should be used with emphasis and reassurance as often as needed to erase all traces of fear and uncertainty of the future. Visits at this time should be made more frequently and medication and physiotherapy fortified, as required.

There are isolated instances when even a mild tremor, as in a barber, may bring loss of employment, economic hardships, and mental depression, which do not readily respond to psychotherapy. They are likely to be remedied by programs of trade retraining to be undertaken by the National Parkinson Foundation.

Patients with late and advanced symptoms of bilateral rigidity, akinesia, impairments of gait, and limitations in self-care can likewise be successfully treated by the family physician, provided a secure home environment and proper facilities for physiotherapy are available. Even disabled patients, under suitable home conditions, will respond favorably to kind words of emotional support and encouragement. Among the latter, however, a more frequent occasion arises for the doctor to obtain the help of a psychiatrist, because of a greater tendency toward depression and agitation. Even so, most patients who are depressed by advanced physical deficits have become more or less acclimated to their status over the years; hence, there is very little risk of attempts at self-destruction.

Aside from active psychotherapy, the doctor's personal interest, enthusiasm, and willingness to see the patient frequently may operate as powerful indirect forces to bolster the patient's morale. The family doctor is often the patient's last recourse for psychotherapeutic help. Many patients dread the prospect of having to go to a psychiatrist because of the inescapable implication that there is something wrong with their minds or that they are "insane." This alone can nullify all the benefits that might be derived from such a referral. It is different with the family physician, whom they know and trust; hence, he is in a position to accomplish more for them and without the alarm and unnecessary expense of consulting a specialist. Second, if the million or so patients with paralysis agitans were to be suddenly thrust on psychiatrists, there would hardly be enough phychiatrists available for the purpose in the entire country.

The means by which a general practitioner could provide better psychotherapy to 98% of patients with paralysis agitans have been presented. Such psychotherapy is within the training and province of every general practitioner. Probably no more than 2% of these patients who are violently disturbed, agitated, and depressed require the services of a psychiatrist or the use of shock therapy, special tranquilization, or mental hospital programs. The fact that the general practitioner cannot always do as well as he would like to is due to forces beyond his control.

Current Limitations to Better Therapy

Because of the absence of suitable community facilities for physiotherapy and rehabilitation, many of today's patients with advanced symptoms of disease become the disabled, dependent, and helpless patients of tomorrow. It is universally recognized that care and treatment of these patients are beyond the resources of the average family. In some sections of our country, physiotherapy treatment is either nonexistent or, if available, is above the means of the patient and family. Some patients are unable to reach a clinic or doctor's office because of gait impairments and lack of transportation; hence they give up all thought of treatment and deteriorate. General hospitals are usually not available to patients with paralysis agitans because the patients do not constitute material for interesting research or teaching and because they require much nursing and other care. Nursing and convalescent homes do not welcome them because of the extra attention they require. For similar reasons, city and chronic hospitals often reject them. The effect on the morale of the patient is bad and is still worse on the morale of members of the family, who are frequently forced to struggle with the care of such patients under adverse conditions until one or the other breaks under strain. The following instance will illustrate:

A patient, 68 years of age, was in an advanced stage of paralysis agitans and had been treated in my office for the past 15 years. Because of lack of physiotherapy facilities in her area and other neglect she became disabled to a point where it was a severe trial for her husband to bring her, even once in several months. He was a hypertensive cardiac patient who struggled to bring his wife from far away Staten Island, at times exerting himself strenuously to even get her out of the automobile and into the office. More recently, he had to bring her in a wheel chair. The strain was far too much for him, with the result that six months prior to this writing he died. Now the responsibility of the patient's care has fallen to her daughter, who has three children to look after. Thus, every two months, with the help of her husband, she undergoes the ordeal of bringing her badly disabled mother to my office. The patient would gladly have spared her family all this hardship if a suitable place were available for her to go to for care and treatment.

Under existing conditions of community neglect, it is not surprising that some patients, realizing that they are to be an endless burden to their families, with nothing to look forward to in terms of treatment, threaten or attempt suicide and are placed for the remainder of their lives in state hospitals, where they do not belong. These people are not insane but are frustrated by real and unfortunate circumstances.

The treatment of disabled patients and those with advanced disease poses a challenge not only to the patient and family but to the doctor from whom the impossible is expected at times. The solution to the problem rests in a twofold broad approach: (1) early and intensive treatment to prevent the later onset of contractures and deformities and (2) a community program to provide proper rehabilitation for patients with advanced cases and special *facilities for the care of totally disabled ones.*

The Outlook

Within the past year the federal government, the American Medical Association, and other agencies have been awakened to the pressing needs of the rapidly growing numbers of the aged and infirm. This newly aroused interest cannot fail to be ultimately translated into better conditions for care and treatment of patients with paralysis agitans.

When the recently created foundations achieve active support from the public for their programs of better treatment for the afflicted and when vigorous research is directed toward the cause and prevention of the disease, the outlook for the patients will materially improve.

It has been pointed out that the ambulatory patients and those in early stages of the disease afford highly favorable prospects for medical and psychotherapeutic care by the family physician. When better community facilities become available for the care of patients with advanced cases, the current greatest challenge to the successful treatment of paralysis agitans will be removed.

710 W. 168th St. (32).

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USE OF TOLBUTAMIDE IN PARALYSIS AGITANS

PRELIMINARY REPORT

Edwin W. Gates, M.D., Niagara Falls, N. Y.
and
Irving Hyman, M.D., Buffalo

Because a marked diminution of tremor of hands and fingers was noticed in a diabetic receiving tolbutamide, the authors began to use tolbutamide in patients with paralysis agitans. The studies have been continued for a year and a half, and the results have been observed in 15 patients. Eleven of the patients showed considerable reduction of tremor or rigidity or both. In several there was a marked improvement in the mask-like facies, with return of a more normal smile. In several patients, improvement of speech was noted. Care was taken to minimize the psychic effect of a new drug. It was determined that the improvements were not related to hypoglycemia. The significance of these findings is not clearly understood, but the results are consistent and indicate the need for further research on man and animals.

Since the introduction of tolbutamide into the United States in 1955, a vast amount of literature has accumulated on its use in the treatment of diabetes mellitus. However, we have been unable to find any reference describing the effect of tolbutamide on tremor or rigidity of paralysis agitans (Parkinson's disease). In May, 1958, one of us noted a marked diminution in the tremor of the hands and fingers of a 57-year-old diabetic who had been given 1 Gm. of tolbutamide three times a day. We began to use tolbutamide in patients with paralysis agitans and observed the effect on tremor and rigidity. Care was taken to minimize the psychic effect of a new drug. The studies have continued for a year and a half, and we have observed the effects of this drug on 15 patients. In 12 of these patients there was noted either reduction of tremor or rigidity or both. In several patients there was a marked change in the mask-like facies with return of a nearly normal facial expression.

Report of Cases

Case 1.—A 57-year-old man with diabetes had a coarse tremor of the hands and fingers. He was unable to hold a cup of coffee without spilling it, and he was not able to write legibly. He was given 1 Gm. of tolbutamide three times a day before meals. After the drug had been given for three days, it was noted that the patient could drink coffee without spilling it and that he could now write legibly. There was a marked diminution in the tremor. Therapy with tolbutamide was continued; 1 Gm. was given twice daily. Four months later tolbutamide therapy was discontinued, and at the end of 11 days the tremor returned. The patient was again given 1 Gm. of the drug three times daily, and in 48 hours there was marked decrease in the tremor. This patient was also on insulin therapy. Six weeks later, when placebo tablets were substituted for tolbutamide, the tremor returned and

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From the Medical Service, Niagara Falls Memorial Hospital (Dr. Gates) and the Neurological Service, Buffalo General Hospital (Dr. Hyman).

again he could not hold a cup of coffee without spilling it. Tolbutamide was again given, after which improvement in the writing and a marked diminution in the tremor were noted. One month later tolbutamide was again replaced with placebo tablets. Once again the tremor returned and the patient was unable to write legibly. There was then an interval of five months during which he was not seen. He had taken tolbutamide intermittently during this time. The tremor had now returned and was the same as before tolbutamide was given. He was again given the drug in a dosage of 3 Gm. daily, but nausea resulted. However, on a dosage schedule of 1 Gm. twice daily, there was no nausea and the tremor improved though not as much as previously. There had been no hypoglycemia; blood sugar levels, determined repeatedly, were in the range of 200 mg. %.

CASE 2.—A 65-year-old woman had had paralysis agitans for 35 years. Examination showed marked rigidity of the arms, legs, and back. There was only slight voluntary motion in the arms with a little more in the right arm. The speech was a monotone, and the patient talked very little. There was constant pill-rolling motion of fingers, a mask-like facies, and salivation. There was considerable loss of motion in some of the joints. There was flexion of the head. The legs could not be fully extended because of rigidity. The patient was given tolbutamide in a dosage of 1 Gm. three times daily. At the end of 48 hours there was much less rigidity and much improvement in the speech. There was a change in the facial expression and the patient could now smile. The left arm showed much less rigidity and could be used slightly. There was more voluntary motion in the right arm. The legs could now be fully extended. The rigidity of the back was practically absent. Forty-eight hours later the patient had a cerebral thrombosis. Tolbutamide therapy was discontinued, and one week later the symptoms of paralysis agitans were the same as before administration of the drug. The signs of the cerebral thrombosis cleared rapidly, and three weeks after the incident the only residual was slight weakness of the left facial muscles. Tolbutamide was again given in a dosage of 1 Gm. twice daily. There was again diminution of the rigidity in the arms, legs, and back, diminution of the tremor of hands, and a return of more facial expression.

CASE 3.—A 78-year-old woman with a severe case of paralysis agitans had marked rigidity of the arms and legs and a coarse, pill-rolling, rhythmic tremor of the hands and fingers. An antispasmodic drug had been given for some months. This therapy was discontinued and resulted in an increase in rigidity; the patient was unable to get out of bed. Seventy-two hours after starting therapy with tolbutamide in a dosage of 1 Gm. three times a day, the patient was able to get out of bed and walk. The tremor was less marked, and there was considerable decrease in the rigidity. This improvement was greater than that resulting from any antispasmodic drugs.

CASE 4.—A 78-year-old woman had paralysis agitans for six years. In spite of antispasmotic medication she showed marked rigidity of legs and arms, more marked in the left arm. There was salivation, mask-like facies, and a coarse tremor of the hands with typical pill-rolling motion of the fingers. There was flexion of the head. Tolbutamide was given in a dosage of 1 Gm. three times daily for two days and then 1 Gm. twice daily. The antispasmotic drug therapy was continued. Three days after the start of therapy with tolbutamide, there was much less rigidity of the arms and legs, and shortly the patient was crossing her knees, which she had been unable to do for years. She was now able to aid in dressing her hair and could put her hands behind her head. It was noted that she was able to lift her feet better. There was considerable improvement in walking, and the fingers were not as stiff. There was a definite improvement in the facial expression. She has been able to walk up and down stairs with help, while formerly she had to be carried. She has been able to get out to visit an oculist and a dentist.

CASE 5.—A 56-year-old woman had a coarse tremor of the hands which became more marked with use of the hands or toward the end of the day when she was tired. Physical examination, including neurological examination, revealed no significant findings. She was given tolbutamide in a dosage of 1 Gm. three times daily before meals. There was no change in the tremor, and after 10 days the drug therapy was discontinued.

CASE 6.—An 83-year-old man had constant tremor of the hands, so marked that it was only with a great deal of difficulty and much time that he could unbutton his shirt. This had been observed frequently. He had generalized arteriosclerosis and arteriosclerotic heart disease. He was given tolbutamide in a dosage of 1 Gm. three times daily before meals. Three days later there was a marked diminution of the tremor. The patient was now able to unbutton and button his shirt nearly normally. The drug therapy was discontinued, with resulting return of tremor. The drug was again given, with resulting diminution of the tremor, but the results the second time were not as spectacular as the first time.

CASE 7.—A 63-year-old woman with paralysis agitans had rigidity of the extremities and a coarse tremor of the outstretched fingers in spite of antispasmodic medication. Her gait was unstable and she walked slowly. The facies were mask-like. She was given tolbutamide, 1 Gm. three times a day, and five days later she was walking much faster and with much less rigidity. The tremor was gone. There was also a change in the facial appearance with some diminution of the mask-like facies.

CASE 8.—A 74-year-old woman had a severe coarse tremor for several years. Her tremor was so violent that she was unable to care for herself. She also complained of abdominal pain and stiffness in her extremities. Examination showed a thin undernourished woman who had a coarse tremor of the outstretched hands. The tremor decreased on grasping. There was generalized rigidity, and she could not perform alternating movements nor do finger-to-nose or heel-to-shin tests. She had hyperactive tendon reflexes and bilateral Babinski response. Some decrease in position and vibration sense were noted in the feet. There were no masses in the abdomen to explain her complaints. She was unable to stand unaided. Tolbutamide was given in doses of 3 and 2 Gm. per day; there was only minimal, if any, improvement in tremor or rigidity.

Case 9.—A 76-year-old man was admitted to the hospital in a lethargic and confused condition and with evidence of pneumonia. The blood pressure was 100/60 mm. Hg and the pulse rate was 70 per minute. He cooperated poorly during the examination. The pupils were small and the arterioles were narrowed. There was paresis of the right upper and lower extremities from a prior cerebral infarct. Cogwheel rigidity could be demonstrated in all extremities, particularly the left. A coarse rhythmic tremor was noted in the outstretched arms. There was flexion of the head. The results of alternation movements and finger-to-nose tests were poor. He was unable to tie his pajamas. He was given insulin, 10 units before breakfast for three days, with no change. One gram of tolbutamide was given three times one day and then twice daily. By the third day there was considerable improvement. He was almost feeding himself and was assisting in his own care. The next morning he had a hypoglycemic reaction with a fasting blood glucose level of 57 mg.% and had a temporary increase in his right-sided paresis.

Case 10.—A 71-year-old woman had paralysis agitans for over 10 years. She was admitted to the hospital because she had fallen and injured her right shoulder. She was unable to get out of bed without assistance and could not feed herself. She had taken various antispasmodic drugs with only moderate relief of her symptoms. On admission to the hospital she demonstrated marked rigidity in all four extremities. There was a coarse tremor of the right hand. There was a right hemiparesis with increased deep tendon reflexes and, on the right, a Babinski response was noted. No sensory deficit was present. The fundi showed considerable arteriovenous nicking. Her speech was rather monotonous and at times difficult to comprehend. She was given tolbutamide, 1 Gm. three times a day for one day and then 1 Gm. twice daily. She became less rigid and the tremor decreased in intensity. After a few days she was able to feed herself and required much less assistance in daily living tasks, such as dressing and bathing. She could walk unaided after one week of therapy.

Case 11.—A 72-year-old woman was admitted for a fracture of the left femur. She had considerable difficulty with tremor and rigidity for several years. Prior treatment with antispasmodics was ineffective. Examination disclosed generalized arteriosclerosis. She had a coarse regular tremor of the hands and feet. There was generalized rigidity, mask-like facies, and salivation. She was given tolbutamide, 1 Gm. three times daily, but no effect was noted on the rigidity nor the tremor.

Case 12.—A 76-year-old woman had increasing stiffness for about six years. She became so immobile that she was unable to get out of bed. Examination disclosed that, aside from generalized arteriosclerosis, she had marked rigidity in all four extremities. The reflexes were equal and the plantars were normal. No sensory deficit was present. She was unable to feed herself because of the rigidity. A coarse alternating tremor was observed. Because of her lack of response to the usual antispasmodic drugs, she was given tolbutamide, 1 Gm. three times daily and then twice daily. She experienced considerable improvement and, with assistance, was able to feed herself. A definite lightening in her mood was observed, and she became more amenable to discussions of her problems.

Case 13.—A 72-year-old man was admitted to the orthopedic service with a fractured pelvis. He had a history of such increasing stiffness and difficulty in getting about that he became an invalid. When seen in the hospital he was thin and undernourished. His spine was flexed and his hands were in a clenched position. Alternations were poorly done and he was unable to feed himself, get out of bed, or walk. He could not tie his pajamas or put on his shirt. There was evidence of generalized arteriosclerosis. When tolbutamide was administered in the dosage of 1 Gm. three times daily and then twice daily, there was a remarkable improvement. He could get out of bed, take some steps unaided, and feed himself. His rigidity was notably less, and there was a diminution in the tremor. Use of the medicament was discontinued, and there was a prompt return of the rigidity and tremor. When tolbutamide was given again, less effect was noted.

Case 14.—A 78-year-old patient had severe paralysis agitans for several years. There was only mild relief from antispasmodic medications. She was able to get out of bed only with assistance and had difficulty in feeding herself. She could not dress herself nor take care of her personal hygiene. She had generalized arteriosclerosis and a pill-rolling tremor of the hands. The tremor decreased on grasping objects. There was generalized rigidity and the fingers were flexed. The spine had a flexed posture. The reflexes were active and equal with normal plantar responses. Some decrease in the peripheral sensation was noted in the feet. She was given tolbutamide, 1 Gm. three times a day and then twice daily. There was considerable improvement in her ability to get out of bed. She could rise to a standing position and was able to feed herself. She required much less nursing care.

Case 15.—A 57-year-old man was admitted for neurological examination to determine his eligibility for chemopallidectomy. He had shown symptoms of paralysis agitans for 15 years and had not shown any response to the antispasmodic medicaments. On examination he was depressed and had a mask-like expression. There was a flexion deformity of the hands and generalized rigidity. A coarse tremor was present in the outstretched hands. He could barely bring his finger to his nose. He was given tolbutamide, 1 Gm. three times daily, and had a marked decrease in rigidity and tremor but no change in mood.

Comment

We suggest that all patients who are given tolbutamide for paralysis agitans be fed six times daily, three meals and three lunches; or each lunch may be replaced with 6 oz. of orange juice. Only one of our patients had a hypoglycemic reaction; this man was undernourished and not taking food very well. In some patients there was a decrease in tremor, and in others the most marked effect was the lessening of the rigidity. Most of the patients given tolbutamide were benefited to the extent that they required less care and could perform many more daily living tasks. Discontinuing the medication and restarting it had varying results, some patients showing benefits and others demonstrating less effect. The effect was not related to hypoglycemia and was present whether or not the patient was given antispasmodic medicaments. In one patient placebos were given and there was prompt return of rigidity and tremor. Most of the patients were not told that the pills would help their symptoms, so the element of suggestion was reduced. We feel that an objective set of tests are in order and also contemplate producing parkinsonian states in animals and administering varying doses of tolbutamide by injection so that the dose and effect can be controlled.

Summary

Tolbutamide was administered to 15 patients with long-standing paralysis agitans (Parkinson's disease). Eleven showed considerable decrease in rigidity and tremor or both. Several showed marked improvement in the mask-like facies with return of a more normal smile. In several patients, improvement of speech was noted. These improvements were not related to hypoglycemia. The significance of these findings is not clearly understood. The results were consistent and indicate the need for further research on man and animals.

625 6th St. (Dr. Gates).

OBSERVATIONS ON LIVE INFLUENZA VACCINE

Gordon Meiklejohn, M.D., Denver

The influenza vaccines developed in the United States since 1940 have been inactivated virus vaccines given by subcutaneous, intradermal, or intramuscular injection. Protection of very high degree has been conferred on vaccinated persons, but no satisfactory solution of many of the problems involved in immunization against influenza has been found. Meanwhile, workers in Russia have concentrated their efforts on live vaccines, with use of attenuated virus strains administered by the respiratory route. Russian vaccines have not previously been tested in the United States. This report presents observations on the responses of 27 volunteers who received live vaccine in the fall of 1958.

Material and Methods

Vaccine.—The vaccine used in this study was prepared at the Metchnikov Institute in Moscow and was received through the good offices of the National Institutes of Health. It was a lyophilized suspension of the fourth allantoic passage of the Iksha (A_2) strain. When resuspended in distilled water and titrated by the allantoic route in chick embryos, it contained $10^{-4.5}$ embryo-infective doses (EID_{50}) per 0.1 ml.

Subjects.—Members of the staff and student body of the University of Colorado School of Medicine served as volunteers for the vaccination studies. Most of them were young adults, and all were symptom-free at the time of inoculation.

Administration of Vaccine.—Subjects lay on their backs on an examining table, with their heads hanging over the end of the table. One-quarter milliliter of vaccine was dropped into each nostril, and the subject was instructed to hold this position for at least one minute, sniffing vigorously.

Laboratory Methods.—Throat washings were collected in beef heart extract broth on the first and second days after inoculation from all subjects, and also on the third and fourth days from 13 subjects. These were frozen at −45 C and subsequently inoculated by both the amniotic and allantoic routes into

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From the Department of Medicine, University of Colorado School of Medicine.

10-or-11-day-old chick embryos. Hemagglutination tests were carried out by means of the technique used by the World Health Organization (WHO),[1] both with the parent nonavid-Iksha strain and with the avid strain, Japan 305. The Japan-305 line used in this study had been passed through ferrets and mice before being propagated serially in chick embryo. Serums were periodate-treated.[2]

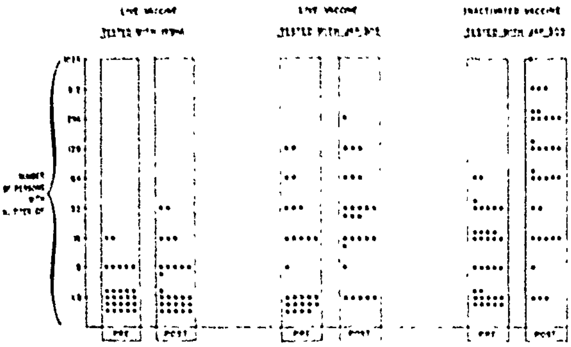

Fig. 1.—Hemagglutination-inhibiting (HI)-antibody titers before and two weeks after vaccination in tests with Iksha and Japan 305 strains.

Results

Clinical Observations.—All subjects reported at the laboratory daily for four days after vaccination. None showed significant elevation of body temperature, and none had symptoms referable to the vaccination.

Recovery of Virus.—Virus was recovered from the throat washings of 3 of the 27 vaccinated subjects. In one person the recovery was from the washing collected on the first day, but washings collected on the second and subsequent days were negative. With the other two subjects, virus was present in washings taken on the second day, but not in those of the first day. In each case virus was recovered in both allantoic and amniotic fluids. Each of these three subjects showed an increase in antibody titer from <1:8 to 1:32.

Hemagglutination-Inhibiting Antibody Response.—The distribution of hemagglutination-inhibiting (HI) antibody titer before and two weeks after vaccination is shown in figure 1. Fourteen of the 27 persons had titers of <1:8 prior to vaccination, while the remaining 13 had antibody in measurable amounts. After vaccination, there was a slight upward shift in the level of antibody titers. This resulted almost entirely from the development of antibody in these subjects who had shown none prior to vaccination (fig. 2). Nine of the 14 persons with titers of <1:8 showed increases in antibody titer of from 2-fold to 32-fold. Of the 13 subjects with titers of 1:8 or more, only 2 showed a fourfold rise, 3 showed a twofold rise, and the remaining 8 showed none. The nonavid character of the Iksha strain in the vaccine is also illustrated in figure 1, in which titers obtained in tests with both the Iksha strain and the avid Japan-305 strain are presented.

In figure 2 the antibody levels before and after vaccination of a similar group of 35 subjects who had received a subcutaneous injection of a polyvalent aqueous vaccine containing 100 chick cell-agglutination (CCA) units of Asian vaccine (Japan 305) are compared to those obtained with the live vaccine. The responses of persons who had titers of <1:8 were of the same order with both vaccines; however, the responses of subjects who had demonstrable levels of antibody differed. With the inactivated vaccine a sharp booster effect was observed, while with the live vaccine the change in antibody titer was relatively insignificant.

Comment

The vaccine used in this study met certain of the criteria set forth by Smorodintsev and Zhdanov in 1957.[3] The infectivity titer of $10^{-5.5}$ per milliliter was close to their recommended level of 10^{-6} per milliliter. Nine of the 14, or more than 50% of the subjects with titers of <1:8, were shown to have an increase in antibody titer after vaccination. However, virus was recovered from only 3 of 14 "susceptible" persons, a proportion which falls considerably short of Smorodintsev's and Zhdanov's criterion that virus should be recovered from 50% of "susceptible" vaccinated subjects. Hence it is possible that the vaccine was below optimal standards in terms of antigenicity, or that the method of administration was faulty. In terms of safety, there was no evidence that the vaccine caused illness.

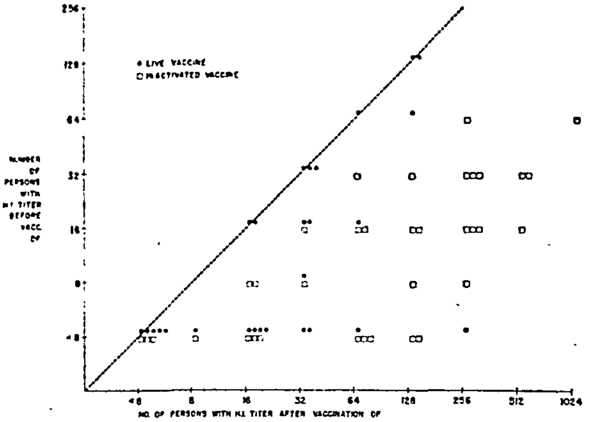

Fig. 2.—Distribution of prevaccination and postvaccination HI-antibody titers of recipients of live and inactivated vaccines.

With respect to effectiveness in evoking an antibody increase in subjects with titers of <1:8, the live vaccine was no better than an inactivated vaccine which was administered subcutaneously and contained only 100 CCA units. In producing a booster effect in persons who had antibody before vaccination, the live vaccine appeared to be inferior to the inactivated vaccine. While the data presented here tend to support the generally held toms of paralysis agitans for 15 years and had not shown any response to the antispasmodic medicaments. On examination he was depressed and had a mask-like expression. There was a flexion deformity of the hands and generalized rigidity. A coarse tremor was present in the outstretched hands. He could barely bring his finger to his nose. He was given tolbutamide, 1 Gm. three times daily, and had a marked decrease in rigidity and tremor but no change in mood.

Comment

We suggest that all patients who are given tolbutamide for paralysis agitans be fed six times daily, three meals and three lunches; or each lunch may be replaced with 6 oz. of orange juice. Only one of our patients had a hypoglycemic reaction; this man was undernourished and not taking food very well. In some patients there was a decrease in tremor, and in others the most marked effect was the lessening of the rigidity. Most of the patients given tolbutamide were benefited to the extent that they required less care and could perform many more daily living tasks. Discontinuing the medication and restarting it had varying results, some patients showing benefits and others demonstrating less effect. The effect was not related to hypoglycemia and was present whether or not the patient was given antispasmodic medicaments. In one patient placebos were given and there was prompt return of rigidity and tremor. Most of the patients were not told that the pills would help their symptoms, so the element of suggestion was reduced. We feel that an objective set of tests are in order and also contemplate producing parkinsonian states in animals and administering varying doses of tolbutamide by injection so that the dose and effect can be controlled.

Summary

Tolbutamide was administered to 15 patients with long-standing paralysis agitans (Parkinson's disease). Eleven showed considerable decrease in rigidity and tremor or both. Several showed marked improvement in the mask-like facies with return of a more normal smile. In several patients, improvement of speech was noted. These improvements were not related to hypoglycemia. The significance of these findings is not clearly understood. The results were consistent and indicate the need for further research on man and animals.

625 6th St. (Dr. Gates).

OBSERVATIONS ON LIVE INFLUENZA VACCINE

Gordon Meiklejohn, M.D., Denver

The influenza vaccines developed in the United States since 1940 have been inactivated virus vaccines given by subcutaneous, intradermal, or intramuscular injection. Protection of very high degree has been conferred on vaccinated persons, but no satisfactory solution of many of the problems involved in immunization against influenza has been found. Meanwhile, workers in Russia have concentrated their efforts on live vaccines, with use of attenuated virus strains administered by the respiratory route. Russian vaccines have not previously been tested in the United States. This report presents observations on the responses of 27 volunteers who received live vaccine in the fall of 1958.

Material and Methods

Vaccine.—The vaccine used in this study was prepared at the Metchnikov Institute in Moscow and was received through the good offices of the National Institutes of Health. It was a lyophilized suspension of the fourth allantoic passage of the Iksha (A_2) strain. When resuspended in distilled water and titrated by the allantoic route in chick embryos, it contained $10^{-4.5}$ embryo-infective doses (EID_{50}) per 0.1 ml.

Subjects.—Members of the staff and student body of the University of Colorado School of Medicine served as volunteers for the vaccination studies. Most of them were young adults, and all were symptom-free at the time of inoculation.

Administration of Vaccine.—Subjects lay on their backs on an examining table, with their heads hanging over the end of the table. One-quarter milliliter of vaccine was dropped into each nostril, and the subject was instructed to hold this position for at least one minute, sniffing vigorously.

Laboratory Methods.—Throat washings were collected in beef heart extract broth on the first and second days after inoculation from all subjects, and also on the third and fourth days from 13 subjects. These were frozen at −45 C and subsequently inoculated by both the amniotic and allantoic routes into

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From the Department of Medicine, University of Colorado School of Medicine.

10-or-11-day-old chick embryos. Hemagglutination tests were carried out by means of the technique used by the World Health Organization (WHO),[1] both with the parent nonavid-Iksha strain and with the avid strain, Japan 305. The Japan-305 line used in this study had been passed through ferrets and mice before being propagated serially in chick embryo. Serums were periodate-treated.[2]

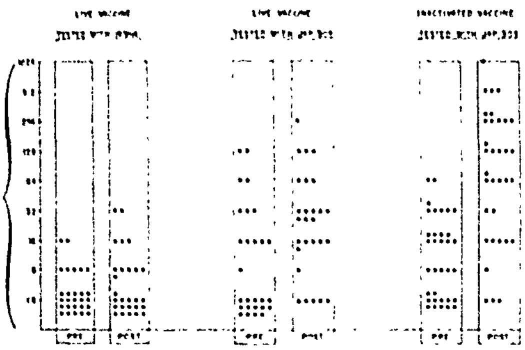

Fig. 1.—Hemagglutination-inhibiting (HI)-antibody titers before and two weeks after vaccination in tests with Iksha and Japan 305 strains.

Results

Clinical Observations.—All subjects reported at the laboratory daily for four days after vaccination. None showed significant elevation of body temperature, and none had symptoms referable to the vaccination.

Recovery of Virus.—Virus was recovered from the throat washings of 3 of the 27 vaccinated subjects. In one person the recovery was from the washing collected on the first day, but washings collected on the second and subsequent days were negative. With the other two subjects, virus was present in washings taken on the second day, but not in those of the first day. In each case virus was recovered in both allantoic and amniotic fluids. Each of these three subjects showed an increase in antibody titer from <1:8 to 1:32.

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In figure 2 the antibody levels before and after vaccination of a similar group of 35 subjects who had received a subcutaneous injection of a polyvalent aqueous vaccine containing 100 chick cell-agglutination (CCA) units of Asian vaccine (Japan 305) are compared to those obtained with the live vaccine. The responses of persons who had titers of <1:8 were of the same order with both vaccines; however, the responses of subjects who had demonstrable levels of antibody differed. With the inactivated vaccine a sharp booster effect was observed, while with the live vaccine the change in antibody titer was relatively insignificant.

Comment

The vaccine used in this study met certain of the criteria set forth by Smorodintsev and Zhdanov in 1957.[3] The infectivity titer of $10^{-5.5}$ per milliliter was close to their recommended level of 10^{-6} per milliliter. Nine of the 14, or more than 50% of the subjects with titers of <1:8, were shown to have an increase in antibody titer after vaccination. However, virus was recovered from only 3 of 14 "susceptible" persons, a proportion which falls considerably short of Smorodintsev's and Zhdanov's criterion that virus should be recovered from 50% of "susceptible" vaccinated subjects. Hence it is possible that the vaccine was below optimal standards in terms of antigenicity, or that the method of administration was faulty. In terms of safety, there was no evidence that the vaccine caused illness.

With respect to effectiveness in evoking an antibody increase in subjects with titers of <1:8, the live vaccine was no better than an inactivated vaccine which was administered subcutaneously and contained only 100 CCA units. In producing a booster effect in persons who had antibody before vaccination, the live vaccine appeared to be inferior to the inactivated vaccine. While the data presented here tend to support the generally held

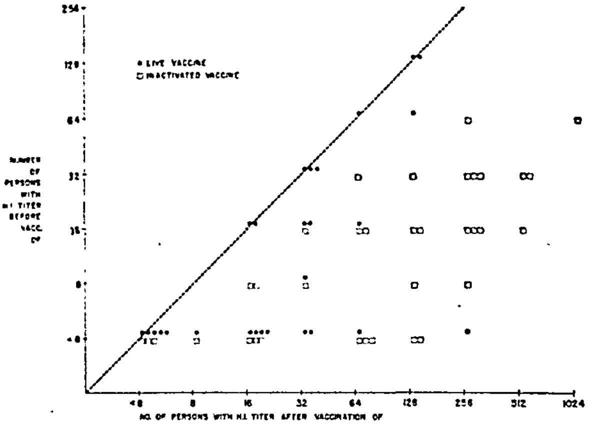

Fig. 2.—Distribution of prevaccination and postvaccination HI-antibody titers of recipients of live and inactivated vaccines.

opinion that inactivated vaccines are preferable to live vaccines, it seems advisable to conduct further comparative studies in laboratories in the United States.

Summary

Live Russian influenza A_2 vaccine, given intranasally, was moderately effective in raising hemagglutination-inhibiting (HI) antibody levels in persons who had no detectable antibody, but persons with antibody showed little booster effect. Inactivated vaccine given subcutaneously was far more effective than the live vaccine in raising antibody levels of persons who had antibody at the time of vaccination. No illness was observed in persons vaccinated with live vaccine.

4200 E. Ninth Ave.

These studies were supported by a contract from the Commission on Influenza, Armed Forces Epidemiological Board, with the U. S. Army Research and Development Command.

Florence Lester and Helen Hemmingsen provided technical assistance for this study. The Japan 305 influenza-virus strain used in this study was supplied by Miss Elva Minuse, School of Public Health, University of Michigan, Ann Arbor, Mich.

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OCCURRENCE OF ALLERGIC DISEASE IN PATIENTS WITH ADRENAL CORTICAL HYPOFUNCTION

Haddon M. Carryer, M.D., Donald W. Sherrick, M.D.
and
Clifford F. Gastineau, M.D., Rochester, Minn.

Data from 27 patients were analyzed in order to determine the relation of adrenal cortical hypofunction to the occurrence of allergic disorders. This group was selected on the basis of evidence of allergic disease, obtained either from the case record or from a personal interview, out of a total of 496 who had been found to have adrenal cortical hypofunction. Among the 496 there were 18 in whom the existing allergic disease showed no correlation with adrenal cortical function and 27 in whom there was (1) a definite time-relation between full development of the hypofunction and appearance or intensification of the allergic disorder or (2) improvement in the allergic disorder as treatment for adrenal cortical hypofunction was implemented. The latter most commonly were in the form of atopic reactions. In 8 of the 27 patients with adrenal cortical hypofunction the administration of cortisone or adrenal extracts ameliorated the atopic symptoms.

It has long been recognized that the adrenal cortex influences reactions of hypersensitivity. Depriving an animal of a functioning adrenal cortex by adrenalectomy or causing adrenal cortical atrophy by hypophysectomy measurably increases the sensitivity of the animal to anaphylactic shock.[1] More recently, hormones of the adrenal cortex, hormones similar to those elaborated by the adrenal cortex, and ACTH, which stimulates the outpouring of adrenal cortical hormones, have all been shown to influence favorably various allergic diseases.[2]

The occurrence of allergic disease was reviewed in a recent study of 101 patients who had adrenal cortical hyperfunction (Cushing's syndrome).[3] Patients with hay fever and bronchial asthma, as well as adrenal cortical hyperfunction, experienced an amelioration of allergic symptoms when adrenal cortical hyperfunction occurred. Conversely, with the surgical correction of adrenal cortical hyperfunction, the allergic disorder recurred.

From the Section of Medicine, Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Read in the Session on Allergy before the Section on Miscellaneous Topics at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

Present Study

We reviewed data on the occurrence of allergic disorders among patients who had adrenal cortical hypofunction (Addison's disease). For this study we had access to the case records of 496 patients who were found to have adrenal cortical hypofunction at the Mayo Clinic from 1915 through 1957. We either reviewed the case records or interviewed and examined these patients to ascertain the presence or absence of allergic disease. If allergic disease was present, we also determined the pattern it assumed and whether it was associated with or influenced by adrenal cortical hypofunction. Because the patients included in the series were seen at the Mayo Clinic over many years, the majority of facts were elicited from a review of medical records.

TABLE 1.—*Chronological Relationship Between Onset of Adrenal Cortical Hypofunction and Allergic Disease in Forty-five Cases*

Allergic Reaction	Related	Not Related
Atopic	17	10
Drug	8	8
Both	2	...
Total	27	18

At the beginning of this study it was recognized that certain problems would be encountered. Foremost among these was the fact that, in the era under consideration, striking changes in the management of adrenal cortical hypofunction were taking place. Patients who had the disease in earlier years under study were uniformly in a serious condition and soon died. The changing efficacy of treatment for this disease is of great importance to the present study. Treatment for adrenal cortical hypofunction progressed through an era of use of weak adrenal cortical extracts to one of use of substances more effective primarily in mineral metabolism and ultimately to use of cortisone and similar drugs. Current clinical and experimental data have demonstrated that the antiallergic influences of steroid drugs are more intimately linked with the anti-inflammatory steroid hormones than with those hormones that primarily induce effects on mineral metabolism.

The records of some patients with adrenal cortical hypofunction were brief and information concerning associated medical problems was limited. This was particularly true in the earlier years. Often the patients were first observed in a state of desperate illness, thereby limiting the opportunity for completion of their recorded medical histories. Information recorded was mainly concerned with the critical problem at hand, namely, adrenal cortical hypofunction. Inquiry about other medical problems including allergic disorders, therefore, was often incomplete. More recent records have served better in providing information as to allergic disorders.

Another problem encountered was the necessity for arbitrarily deciding the time of onset of adrenal cortical hypofunction. The onset of this disease usually is insidious. Before a diagnosis was established and before medical attention was sought, many patients experienced a period of gradual weakness, loss of weight, or other symptoms suggesting, in retrospect, that these were indeed early evidences of adrenal cortical hypofunction. Since it was our wish to correlate the occurrence of allergic disorders with adrenal cortical hypofunction, it became necessary to make, on occasion, assumptions that symptoms occurring before overt signs of adrenal cortical hypofunction were actually harbingers of that disease.

It was necessary to decide, at times rather arbitrarily, whether cortisone was being given only in physiological replacement amounts or in amounts so large as to implement a pharmacological suppression of allergic manifestations. The distinction is probably a quantitative one only, inasmuch as amounts of cortisone corresponding to the normal adrenal production of cortisone-like hormones are similarly capable of suppression to a degree of the allergic process.

The purpose of this study was to compare the degree of allergy exhibited by these persons with an allergic diathesis before and after the development of adrenal insufficiency. The effect of therapy for adrenal cortical hypofunction on the allergic state was also considered.

Results

Of 496 patients with adrenal cortical hypofunction, 451 had no recorded history or finding of associated allergic disease, and 45 had a history or findings suggesting one or another type of allergic disorder, such as asthma, hay fever, urticaria, angioedema, perennial allergic rhinitis, or drug allergy (table 1).

TABLE 2.—*Effect of Onset and Treatment of Adrenal Cortical Hypofunction on Allergic Disease*

	Atopic Disease	Drug Allergy
Onset of allergic disease		
Before adrenal cortical hypofunction	7	1
Near or after adrenal cortical hypofunction	12	9
Effect of onset of adrenal cortical hypofunction		
Worsening	5	1[*]
No change	2	
Effect of treatment of adrenal cortical hypofunction		
Patients studied	8	10
Improved	8	1[†]
Not improved		1[‡]
No effect established		8

[*] In nine patients an allergic reaction to a drug occurred after the onset of adrenal cortical hypofunction.
[†] Improvement questionable.
[‡] Treatment with desoxycorticosterone acetate.

In 18 of the 45 patients with allergic disease no correlation was found to exist between the adrenal cortical hypofunction and the allergy. Indeed, if any relationship existed, inadequate data were available to establish that relationship. Among

TABLE 3.–*Data Concerning Patients with Both Adrenal Cortical Hypofunction and Allergic Disease*

	Adrenal Cortical Hypofunction						Treatment for Adrenal Cortical Hypofunction	
	Onset		Initial Visit					
Case No.	Age	Sex	Yr.	Age	Allergic Disease	Time of Onset of Allergic Disease in Relation to Onset of Adrenal Cortical Hypofunction	At Time of Allergic Symptoms	Effect on Allergic Symptoms
1	31	F	1930	32	Perennial allergic rhinitis	Perennial allergic rhinitis 2 yr. before, moderately severe at onset of adrenal cortical hypofunction	Extract of adrenal cortex (Swingle's extract)	. . .
2	46	M	1931	49	Bronchial asthma; chronic urticaria	Bronchial asthma and chronic urticaria 2½ yr. after first pigmentation	Extract of adrenal cortex (Swingle's extract)	. . .
3	44	M	1932	44	Drug allergy, with beginning exfoliative dermatitis, to emetine or methenamine derivative of meta-amino para-oxyphenylarsonic acid (Treparsol) or both for parasitic infestation	Allergic reaction after fully developed adrenal cortical hypofunction	None until allergic reaction rapidly spread, extract of adrenal cortex (Eschatin), 10 cc. daily, after onset of skin eruption	What appeared to be rapidly developing exfoliative dermatitis subsided with stopping antiparastitic medications and/or use of extract of adrenal cortex
4	43	M	1934	45	Drug allergy to anterior pituitary extract; urticaria on 3rd injection	Allergic reaction after fully developed adrenal cortical hypofunction	10 cc. of adrenal cortical hormone by injection	. . .
5	32	F	1934	32	Drug allergy to sesame oil used as vehicle for desoxycorticosterone acetate; urticarial response; tolerated peanut oil as vehicle	Allergic reaction after fully developed adrenal cortical hypofunction	Desoxycorticosterone acetate, on preceding day 125 mg. of corticosterone by injection	. . .
6	28	M	1937	29	Chronic urticaria and angioedema	Allergic disease 6 mo. prior to early manifestations of adrenal cortical hypofunction	None	. . .
7	35	F	1939	40	Chronic urticaria	Urticaria briefly at age 11, chronic urticaria at time pigmentation developed at age 38, after 3 yr. of increasing weakness	None	. . .
8	31	F	1940	36	Perennial allergic rhinitis, onset at age 33; two isolated episodes of asthma at ages 33 and 36	Perennial allergic rhinitis after early manifestation of adrenal cortical hypofunction; two isolated episodes of asthma prior to and after diagnosis of adrenal cortical hypofunction	Desoxycorticosterone acetate by injection; sodium chloride orally	. . .
9	32	F	1940	33	Urticaria, cause undetermined (1 wk. duration)	Urticaria 2 yr. after onset of adrenal cortical hypofunction	Suprarenal preparation, cortin, 5 cc. daily, desoxycorticosterone acetate, 1 mg. daily, and sodium chloride	. . .
10	52	M	1940	52	Perennial allergic rhinitis 2 yr. before early manifestation of adrenal cortical hypofunction; nasal polypectomy required	Perennial allergic rhinitis with recurrent nasal polyps at time adrenal cortical hypofunction was diagnosed	Desoxycorticosterone acetate and sodium chloride	Nasal polypi present 6 mo. after treatment with desoxycorticosterone acetate and sodium chloride; nasal symptoms no longer a problem when seen at age 54 and age 58
11	52	M	1942	52	Bronchial asthma from 46 years of age	Mild bronchial asthma until age 52, moderately severe, with early manifestations of adrenal cortical hypofunction	Desoxycorticosterone acetate and sodium chloride. Adrenal cortical extract	Mild asthma persisted, congestive heart failure developed
12	30	F	1946	32	Drug allergy to penicillin, with skin eruption after its use for urinary tract infection	Allergic reaction 1 yr. after early symptoms of adrenal cortical hypofunction	None	. . .
13	40	M	1946	46	Drug allergy to concentrated liver extract for pernicious anemia at age of 36; urticarial drug reaction	Allergic reaction to liver extract at age 38, with desensitization, was tolerated several weeks; then not tolerated; recurred	Desoxycorticosterone acetate, 2 mg. daily by injection	Urticaria after injections of liver extract continued
14	49	F	1948	49	Drug allergy to penicillin and/or chlortetracycline, with edema and cheilitis after drugs for respiratory infection	Allergic reaction occurred after fully developed adrenal cortical hypofunction; reaction when control of adrenal cortical hypofunction was poor	Implants of desoxycorticosterone acetate	. . .
15	20	F	1948	21	Drug allergy with urticaria after intravenous injection of medium in excretory urography	Reaction a few weeks after early manifestation of adrenal cortical hypofunction	None	. . .
16	31	M	1948	32	Urticaria and angioedema; drug allergy after sulfadiazine and penicillin therapy; urticaria and angioedema 5 days after administration of sulfadiazine and 3 days after administration of "sulfa-penicillin" tablet	Urticaria and angioedema recurrently at age 20 to 27 prior to adrenal cortical hypofunction; drug allergy with urticaria during treatment for adrenal cortical hypofunction	Desoxycorticosterone acetate (Percorten) 0.4 cc. intramuscularly, daily	. . .
17	59	F	1948	60	Mild recurring bronchial asthma from age 44, mainly after upper respiratory infections	Asthma present 15 yr. before onset of adren [illegible] chang [illegible] time [illegible] developed	Lipoadrenal extract, 0.5 to 1 cc. daily + desoxycorticosterone acetate, 2 mg. daily	With treatment asthma virtually controlled. Recurrence on omitting treatment.
18	29	M	1948	30	Severe bronchial asthma requiring hospitalization for severe nightly attacks	Asthma 6 mo. after onset of adrenal cortical hypofunction	Desoxycorticosterone acetate + lipoadrenal extract, 0.5 cc. daily	In 2 weeks asthma virtually controlled
19	53	F	1949	54	Childhood asthma, onset of seasonal hay fever at age 33, gradually abating in several years thereafter	Mild recurrence of hay fever 4 yr. before and severe recurrence of hay fever 1 yr. before onset of adrenal cortical hypofunction	Desoxycorticosterone acetate (Cortate), 2 mg. daily	. . .

TABLE 3.—*Data Concerning Patients with Both Adrenal Cortical Hypofunction and Allergic Disease—Continued*

	Adrenal Cortical Hypofunction						Treatment for Adrenal Cortical Hypofunction	
	Onset		Initial Visit					
Case No.	Age	Sex	Yr.	Age	Allergic Disease	Time of Onset of Allergic Disease in Relation to Onset of Adrenal Cortical Hypofunction	At Time of Allergic Symptoms	Effect on Allergic Symptoms
20	37	F	1949	42	Bronchial asthma	Onset of chronic cough, age 39, 2 yr. after onset of adrenal cortical hypofunction; associated bronchial asthma at age 42	None	. . .
21	42	M	1950	42	Chronic urticaria, mainly nocturnal, 4 to 5 nights a week	Chronic urticaria 4 yr. after onset of adrenal cortical hypofunction	25 mg. of cortisone divided into 4 doses daily; buccal administration of desoxycorticosterone acetate 2 mg. daily; also buccal administration of testosterone, 10 mg. daily	. . .
22	39	F	1951	40	Perennial allergic rhinitis	Rhinitis 9 mo. after early manifestation of adrenal cortical hypofunction	None	. . .
23	37	F	1951	42	Chronic urticaria and angioedema; drug allergy to foreign serum, aspirin, aminopyrine and concentrated liver extract with urticaria and/or angioedema after their use	Urticaria and angioedema occasionally for 13 yr. prior to early symptoms (exhaustion); severe for 6 mo. before definite symptoms of adrenal cortical hypofunction	Cortisone, 37.5 mg. daily; later 30 mg. daily; 2 mg. of buccally administered desoxycorticosterone acetate added later; fludrocortisone acetate (Florinef), 0.2 mg., substituted for desoxycorticosterone acetate later	Chronic urticaria and angioedema controlled by controlling adrenal cortical hypofunction with this amount of cortisone. Only one recurrence (for 2 wk.) in ensuing 3 yr. No record of contact with drugs
24	27	F	1952	35	Bronchial asthma and perennial allergic rhinitis	Bronchial asthma and perennial allergic rhinitis at age 35 at time of deepening of previously mild pigmentation (present from age 27)	Cortisone 20 mg. daily; also buccally administered desoxycorticosterone acetate, 4 mg. daily	Bronchial asthma essentially controlled (one attack in 3 yr. after a respiratory infection)
25	36	M	1952	36	Drug allergy to penicillin (urticaria), nitrofurazone (dermatitis venenata), chloramphenicol (stomatitis)	No allergic symptoms until about 1 yr. after onset of adrenal cortical hypofunction	Cortisone, 15 mg. daily + fludrocortisone acetate, 0.2 mg. daily, or buccally administered desoxycorticosterone acetate, 2 mg. daily	
26	45	M	1953	47	Bronchial asthma	Bronchial asthma 1 mo. after early symptoms of adrenal cortical hypofunction	None at time asthma occurred for 18 mo; later cortisone, 20 mg. daily, and either buccally administered desoxycorticosterone acetate, 6 mg. daily, or 0.1 mg. of fludrocortisone daily	Bronchial asthma subsided to chronic cough after 18 mo.; with treatment for adrenal cortical hypofunction cough subsided; no respiratory complaints at examination at age 49, 50, and 52
27	60	F	1954	61	Bronchial asthma since age 15; mild after age 28; only 2 mild attacks a year after respiratory infection	Bronchial asthma more severe at age 60 with initial symptoms of adrenal cortical hypofunction	Cortisone, 30 mg. daily, and desoxycorticosterone acetate, 4 mg., sublingually daily (latter drug later supplanted by fludrocortisone)	Bronchial asthma improved

these 18 patients 8 had drug reactions and 10 had atopic disease. This group will not be considered further in this report.

In 27 of the 45 patients the allergic disorder (1) developed long before and was worse after the onset of adrenal cortical hypofunction, (2) developed so near the time of onset as to suggest that adrenal cortical hypofunction might have been present, (3) was first evident after adrenal cortical hypofunction was fully developed, or (4) appeared to be influenced by therapy for adrenal cortical hypofunction. In these 27 patients the allergic reaction was considered to be definitely related to the adrenal cortical hypofunction. In 17 of these patients, the reaction was atopic and assumed the form of asthma, hay fever, urticaria, angioedema, or perennial allergic rhinitis. In eight patients the reaction was a drug reaction. Two patients exhibited hypersensitivity of both types.

Of the patients who showed a correlation between the occurrence of adrenal cortical hypofunction and various reactions of hypersensitivity, 12 were male and 15 were female. Evidences of adrenal cortical hypofunction first developed at the average age of 40 years and 8 months. The allergic diseases encountered included drug allergy in 10 cases, bronchial asthma in 10, urticaria or angioedema in 7, perennial allergic rhinitis in 5, and hay fever in 1.

Among patients with atopic forms of hypersensitivity, seven had had allergic manifestations long before adrenal cortical hypofunction occurred. Twelve had atopic symptoms either shortly before, suggesting that adrenal disease may have been beginning, or soon after adrenal cortical hypofunction was fully developed. With one exception (case 23) all allergic reactions to drugs followed the onset of classic addisonian symptoms (table 2).

Among the seven patients who had atopic reactions antedating adrenal cortical hypofunction, there were five in whom the severity of allergic symptoms was accentuated coincidentally with the onset or intensification of the disease. The allergic status of the other two patients was improved after replacement therapy for adrenal cortical hypofunction.

The establishment of a correlation between the occurrence of drug allergy and adrenal cortical hypofunction posed many problems. In many instances there was little basis for a comparison of reactions under different circumstances, for such isolated reactions were frequently single. They had usually taken place prior to the institution of treatment for adrenal cortical hypofunction.

Observations concerning the effect of treatment for adrenal cortical hypofunction on an associated atopic disease were available primarily among patients seen later in the series. In all eight cases in which the effect of treatment with cortisone or adrenal extracts on atopic disease was documented, such treatment was associated with an amelioration of the atopic disorder. In one (case 10) an effect on the improvement of the allergic state is dubious inasmuch as desoxycorticosterone acetate was the agent employed.

A suggestion as to the possible influence of adrenal cortical hypofunction on drug allergy was noted in two patients (cases 3 and 13). In one patient a spreading dermatitis which was assuming exfoliative characteristics was rapidly halted by stopping use of offending drugs and by the administration of extract of adrenal cortex (Swingle's extract). Another patient who tolerated injections of concentrated liver extract poorly continued to do so despite improvement in the control of his adrenal cortical hypofunction. Desoxycorticosterone acetate, which exhibits mainly a mineral effect, was used in the management of that patient.

The study has pointed out a relationship between adrenal cortical hypofunction and various allergic disorders. No attempt has been made to designate that facet of the allergic reaction influenced by the occurrence of adrenal cortical hypofunction.

Details of these 27 cases are given in table 3.

Summary and Conclusions

A study of 496 patients with adrenal cortical hypofunction (Addison's disease) disclosed 45 with allergic disorders. The allergic disorder in 27 of these 45 patients was chronologically associated with Addison's disease or improved after replacement therapy for adrenal cortical hypofunction. Eight of these 27 patients had drug allergy alone, and 17 had atopic disorders such as asthma, hay fever, perennial allergic rhinitis, urticaria, and angioedema. Two patients had both drug allergy and atopic disorders.

Patients with atopic disorders of long standing often experienced an accentuation in the severity of those disorders at the time adrenal cortical hypofunction developed or as it progressed. In each of the eight patients with atopic disorders on whom an appraisal of the influence of replacement therapy for adrenal cortical hypofunction was possible, an amelioration of the atopic disorder occurred. The information was less conclusive concerning an accentuating influence on the occurrence or severity of drug allergy. This study again suggests the role of the adrenal cortex in influencing the course of an allergic diathesis.

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BACTERIOPHAGE TYPING OF STAPHYLOCOCCI FROM ASTHMATIC PATIENTS

SEVENTH OF A SERIES ON BACTERIOLOGICAL AND EPIDEMIOLOGIC APPROACH TO TREATMENT OF SINORESPIRATORY INFECTIONS

Samuel J. Prigal, M.D., New York

The techniques of bacteriophage typing were applied in a study of staphylococci cultured from 115 persons in an effort to detect a possible role that the hemolytic staphylococcus might play in infectious asthma. Ninety-five of the subjects were members of 27 families. A family was classified as "colonized" if two or more of its members yielded staphylococci of the same bacteriophage pattern. Among 12 colonized families the number of persons harboring hemolytic staphylococci, the number of patients with asthma, and the severity of the asthma were all greater than in an equal number of noncolonized families. However, the distribution of staphylococci according to their reaction to bacteriophage typing was the same as that usually seen in the general population, and no one type of staphylococcus could be etiologically related to infectious asthma.

The hemolytic staphylococcus was found, in earlier studies, to be frequently encountered in sinorespiratory infections associated with asthma.[1] Further studies of individual persons and members of families suggested the possibility that sinorespiratory infections, recurrent or chronic, or both, resulted from intrafamilial contagion.[2] A study was undertaken, therefore, to identify more specifically the staphylococci encountered by the method of bacteriophage typing. The use of this procedure, it was hoped, would (1) confirm the earlier evidence suggestive of intrafamilial contagion and of self-reinfection from other infected sites of the body (e. g., skin, eye, and ear), (2) determine whether any special type or types of staphylococci were dominant in these persons and whether they were in any way causally related to infective asthma, (3) demonstrate the manner of spread of the staphylococcic infection, and (4) determine the persistence of the staphylococcus in infections encountered in individual persons and families.

Material and Methods

The procedures involved in bacteriophage typing have been described elsewhere in detail by Blair and Carr [3] and were used by them in this investigation. Twenty-four bacteriophages, classified into five groups and recommended by the International Committee on Bacteriophage Typing of Staphylococci, were used.

In view of the specificity of the lytic action of the bacteriophages, it is possible to identify and "fingerprint" staphylococci, thereby making it an important tool in epidemiologic studies.

Results

Table 1 summarizes the proportion of typable cultures obtained from 27 families and 20 individual subjects in whom sinorespiratory infections were a problem. Altogether, 115 persons were examined and subjected to bacterial culture. The families were selected for bacteriological studies because of the frequency of sinorespiratory infections (often associated with asthma) in one or more members. Many subjects presented no obvious signs of infection. Despite negative physical findings, some of these persons yielded coagulase-positive hemolytic staphylococci and presumably were carriers. Some of the staphylococci, it should be indicated, were also isolated from the eyes or skin of a limited number of patients with pyogenic infections in these areas. In contrast to the families studied, all the individual patients presented positive evidence of infection, usually in several sites.

Of a total of 198 staphylococci available for typing, 164 (82.8%) were found typable, while the 34 others (17.2%) were not. The high degree of typability is accounted for by the repeated cultures taken from the same subject on different occasions or by multiple cultures taken from several sites of infection.

It should be noted that most often the staphylococci were lysed by more than one bacteriophage, in one instance by as many as eight and more frequently by a combination of two or three. When grouped, they fell into a basic pattern as previously described, with a distribution of about 50% in group 3.[3]

The bacteriophage-type pattern of reaction was specially analyzed in 16 patients with asthma, some of whom were asymptomatic at the time of examination but were included in family surveys. In five of these patients, hemolytic staphylococci were encountered which reacted to bacteriophages 52A

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Among the seven patients who had atopic reactions antedating adrenal cortical hypofunction, there were five in whom the severity of allergic symptoms was accentuated coincidentally with the onset or intensification of the disease. The allergic status of the other two patients was improved after replacement therapy for adrenal cortical hypofunction.

The establishment of a correlation between the occurrence of drug allergy and adrenal cortical hypofunction posed many problems. In many instances there was little basis for a comparison of reactions under different circumstances, for such isolated reactions were frequently single. They had usually taken place prior to the institution of treatment for adrenal cortical hypofunction.

Observations concerning the effect of treatment for adrenal cortical hypofunction on an associated atopic disease were available primarily among patients seen later in the series. In all eight cases in which the effect of treatment with cortisone or adrenal extracts on atopic disease was documented, such treatment was associated with an amelioration of the atopic disorder. In one (case 10) an effect on the improvement of the allergic state is dubious inasmuch as desoxycorticosterone acetate was the agent employed.

A suggestion as to the possible influence of adrenal cortical hypofunction on drug allergy was noted in two patients (cases 3 and 13). In one patient a spreading dermatitis which was assuming exfoliative characteristics was rapidly halted by stopping use of offending drugs and by the administration of extract of adrenal cortex (Swingle's extract). Another patient who tolerated injections of concentrated liver extract poorly continued to do so despite improvement in the control of his adrenal cortical hypofunction. Desoxycorticosterone acetate, which exhibits mainly a mineral effect, was used in the management of that patient.

The study has pointed out a relationship between adrenal cortical hypofunction and various allergic disorders. No attempt has been made to designate that facet of the allergic reaction influenced by the occurrence of adrenal cortical hypofunction.

Details of these 27 cases are given in table 3.

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to the mother's side of the family, but the identical staphylococcus was not obtained in any other member.

Case 4.—This case deals with a child with severe asthma and eczema, in whom, for seven years, a coagulase-positive hemolytic staphylococcus was repeatedly cultured from the nose, throat, eye, or skin. Continued use of a variety of antibiotics ultimately led to resistance to each one and to the emergence of a staphylococcus of type 80/81, which was also isolated from an infected ear of the mother. The asthma was further complicated by unusual pulmonary manifestations, presumably due to staphylococcic infection.

A female infant was first seen in December, 1951, at the age of 19 months, because of a generalized ezcema and asthma. From the beginning infection was considered a primary cause of her asthma. A coagulase-positive Staphylococcus aureus was repeatedly obtained from the nose and throat, at times in pure culture but frequently in association with streptococci.

In 1955, the entire family was studied because of repeated infections both in the patient and in other members. Clinically, there was evidence of intrafamilial contagion. Bacteriophage typing, however, revealed that the staphylococci responsible for the symptoms were of unrelated types.

Because of the persistence of the infection in the patient, despite antibiotic therapy, the asthma continued to be moderately severe and cortisone was resorted to for therapy. A high degree of allergy was present in the patient, as shown first by passive transfer test and subsequently by direct testing as well as by clinical observation of sensitivity to many foods, pollens, and inhalants. The asthma became severe with each new

and would impro

another, from the nose and throat, the eczematous skin area, a purulent conjunctivitis, and a gluteal abscess.

In November, 1958, there was an unusual complaint of severe abdominal pain which had followed an acute upper respiratory infection with fever. The pain was, at times, so severe as to make the attending physician suspect an attack of gallbladder disease. The erythrocyte sedimentation rate (Wintrobe) was increased to 51 mm. per hour, and the white blood cell count was 24,000 per cubic millimeter, with an eosinophilia of 10%. The child was hospitalized for study.

Although the asthma was under control and there were no overt chest symptoms, an x-ray of the chest revealed a large emphysematous cyst in the right upper pulmonary lobe (fig. 1, *center, right*). Roentgenographic examination of the sinuses showed bilateral maxillary sinusitis (fig. 2, *right*). (Similar studies performed five months earlier had revealed no pathological findings [fig. 1, *left*, and 2, *left*]). Studies of cultures from the pharynx again revealed coagulase-positive hemolytic staphylococcus.

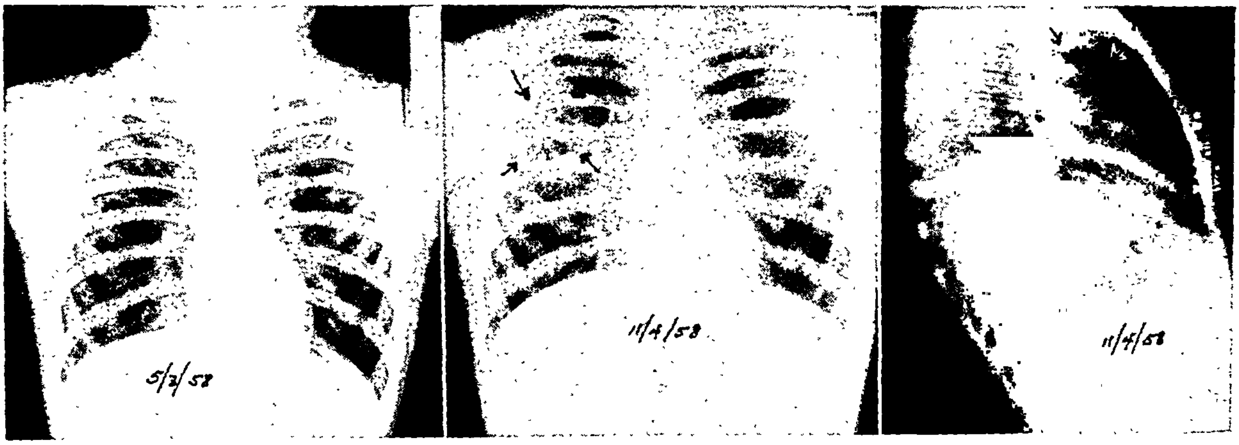

Fig. 1 (case 4).—Chest roentgenograms of asthmatic patient with staphylococcic infection. *Left*, routine chest roentgenogram, May 3, 1958, without abnormalities. *Center*, large emphysematous cyst in right upper pulmonary lobe. *Right*, lateral view of same (Nov. 4, 1958).

Subsequent follow-up studies show a gradual reduction in the cyst to approximately one-third of the original size. In March, 1959, there was a recurrence of the abdominal pain which again could not be accounted for clinically, and an x-ray of the chest once more revealed a small area of consolidation, this time in the left lower lobe (fig. 3). Pharyngeal culture again showed a hemolytic staphylococcus which, on bacteriophage typing, was revealed to be 80/81 and was completely unresponsive to any of the common antibiotics. (The bacteriophage typing pattern in 1954 had been 7/42E/42B/42D/44A and in 1955 39/44A.) New cultures were

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five, and this time hemolytic staphylotion were noted, nor was there any evidence of asthma. However, a slight purulent discharge was visible in the inner canthus of the right eye, without any obvious conjunctivitis.

Laboratory examination showed a slight elevation in the number of leukocytes, without eosinophilia; a nasal smear was unrevealing. Roentgenographic studies of the chest showed an increase of the hilar markings, while those of the sinuses revealed a thickening of the mucosa of the right maxillary antrum, without evidence of any fluid.

The first cultures from the boy's nose, throat, and right eye yielded no pathogens. While under observation, a series of respiratory infections occurred within the family group, including the patient whose asthma was worse and who developed a purulent conjunctivitis from which a hemolytic staphylococcus was cultured. Cultures taken simultaneously from the rest of the family yielded hemolytic staphylococci from the nose, throat, and eye of the mother who had a history of sinusitis, frequent styes, and acneiform skin infections. These organisms, when typed (53/70), were identical with that obtained simultaneously from the patient's eye and were also identical with that cultured from the father's nose. Culture from the father's throat swab yielded a staphylococcus with bacteriophage pattern 75/VA4, while from the younger son, who was also subject to frequent respiratory infections without asthma, a nontypable hemolytic staphylococcus was cultured.

Intradermal skin tests on the patient showed many positive reactions. Only house dust, apple, and white potato were considered clinically important allergens.

Aerosol therapy, in which neomycin sulfate, polymyxin B sulfate, and bacitracin were used in combination, was administered to both the patient and his mother, while the doses of cortisone and orally given antibiotics were simultaneously reduced and then eliminated. Both responded to this treatment; the boy's asthma became less troublesome, while the mother's skin and eye infections improved.

To improve the immunity of both the mother, who presumably was the carrier, and the patient, a vaccine was made of the staphylococcus obtained from the three members of the family, to which was added a stock-mixed catarrhal vaccine. Soon it was noted that minute doses of the vaccine resulted in exacerbations of the boy's asthma. The vaccine was therefore diluted further and the amount given increased cautiously.

At reexamination of the patient in June, 1956, one year after the initial examination, it was disclosed that the incidence of respiratory infections within the household had been reduced, and that the patient had virtually no asthma.

CASE 3.—This case demontsrates the use of bacteriophage typing in the identification of a hemolytic staphylococcus which had colonized a family, three of whose members had asthma, and the transfer of the organism in the process of moving from one apartment to another. This case, described in detail elsewhere,[10] will be reviewed briefly.

A father and his two children, all with asthma in which infection was a factor, had been under observation; on culture, a hemolytic staphylococcus was obtained from them and from one other member of the family. Bacteriophage typing proved all the organisms to be identical, exhibiting the phage pattern 52A/79. The same organism ultimately was cultured from a kitchen plate during an investigation of the dissemination of the staphylococcus within the household. Simultaneously, the new and uninhabited apartment into which the family was moving was investigated, and no hemolytic staphylococci were encountered. Three months after habitation of the new apartment, agar plates were exposed again; the results revealed that the organism had now been transported into the new environment, staphylococci of the same bacteriophage pattern (52A/79) being isolated.

As in the earlier studies of intrafamilial contagion, an investigation was made of the father's six brothers and sisters and their children, as well as of his parents. Many members of the family were subject to frequent colds, sinusitis, bronchitis, asthma, boils, styes, and conjunctivitis. Of 13 cultures obtained from the 22 members of the family, 5 yielded coagulase-positive staphylococci which, however, on bacteriophage typing, differed from the one found in the members of the originally tested family. Bacteriological studies of this family continued over one year, during which time the staphylococcus type 52A/79 persisted in most members.

During one of these examinations, a nephew from the mother's side, who was helping with the children, was at once recognized as a former patient with asthma due to ragweed sensitivity and infection, who had been successfully treated and had remained asthma-free for the past five years. On culture, he yielded a hemolytic staphylococcus of type 52A/79. The investigation then was [illegible] from

TABLE 2.—*Incidence of Hemolytic Staphylococci in Relation to Infectious Asthma in Colonized and Noncolonized Families*

Type of Family*	No. of Families	No. of Individual Members	No. of Persons Showing Hemolytic Staphylococcus	No. of Patients with Asthma	No. of Families with Asthma	Status of Patients with Asthma: Symptomatic	Status of Patients with Asthma: Asymptomatic
Colonized	12	42	36(85.7%)	11(26.2%)	8(66.6%)	9	2
Noncolonized	12	41	21(58.5%)	5(12.2%)	4(33.3%)	1	4

* Colonized families are those in which more than one member in the immediate family showed hemolytic staphylococci of identical bacteriophage pattern. The noncolonized families also showed hemolytic staphylococci, although to a lesser degree, but these were not identical when they occurred in more than one member in the family. At least one member showed a hemolytic staphylococcus, most often the patient.

and 79. No significance can be attached to this, however, since it occurred three times in a single family, once in a close relative, and once in an unrelated subject. This merely reflected colonization of a family by a specific hemolytic staphylococcus. It would seem, therefore, that no specific type of hemolytic staphylococcus may be associated with asthma based on infection, although this organism is frequently encountered in this condition.

The possible role that the hemolytic staphylococcus may play in infectious asthma is shown in the family studies. If one groups them into "colonized" and "noncolonized" families on the basis of the isolation of identical (according to bacteriophage reaction) staphylococci which are present in more than one member of the family, it is apparent that asthma associated with infection occurs more often in colonized families. Table 2 shows that, in a comparison of equal numbers of families and individual subjects who are classified into the aforementioned groups, the colonized group contains twice as many families and patients with asthma as the noncolonized group. Furthermore, the colonized group contained the patients with the worst asthmatic condition; 9 of 11 were symptomatic at the time of culture, whereas only one of five was symptomatic in the noncolonized group.

Table 1.—*Source and Bacteriophage Typing of Hemolytic Staphylococci Isolated from Persons and Families with Sinorespiratory Infections*

Hemolytic Staphylococci		No. of Persons Subjected to Culture	Hemolytic Staphylococci Cultured		
No.	Source		Typable	Non-typable	Total
27	Families	95	139	29	168
20	Individual Patients	20	25	5	30
Totals		115	164(82.8%)	34(17.2%)	198

Report of Cases

The following case histories illustrate the various applications of bacteriophage typing used in this study:

Case 1.—This case demonstrates the role of a father as the carrier for a child with infectious asthma. A 4-year-old boy was first seen in June, 1954, because of asthma after a series of acute upper respiratory infections which had begun in the first weeks of his life when he developed croup. Thereafter he had frequent sore throats and bronchitis through most of the winter. At the age of 2 years he began to wheeze with each of the colds, and in the past year shortness of breath became a prominent symptom to a degree that required an injection of epinephrine for relief. The child's family history disclosed no allergic background. The father had been subject to sinusitis for many years, as well as to bronchopneumonia and croup in childhood.

At examination of the patient, no evidence of asthma was noted. There were, however, findings indicative of a low-grade upper respiratory infection. The membranes of the nose were hyperemic, and the concha nasalis media on the right side was swollen. Stringy mucus was seen bridging the nose on that side. The tonsils were enlarged, the throat was granular, and a postnasal drip was noted. Cervical nodes were palpable bilaterally.

A diagnosis of bronchial asthma based primarily on an infection was made. Results of skin tests with inhalants were negative. Food tests were deferred, since each episode, as observed over a period of several months, was definitely associated with respiratory infection.

A culture taken from the throat at the first examination yielded Staphylococcus citreus, which was nonhemolytic but coagulase-positive. The patient continued to have respiratory infections, and, while they responded to antibiotic therapy, they recurred subsequently. It was decided, therefore, to take cultures from the noses and throats of all members of his family.

On July 27, 1954, a coagulase-negative hemolytic staphylococcus was cultured from the nose and Pseudomonas aeruginosa from the throat of the patient. His sister's culture specimen yielded a hemolytic staphylococcus of bacteriophage type VA4 in association with a nonhemolytic streptococcus. The mother's specimen yielded a staphylococcus of bacteriophage type 29 from the nose. A coagulase-positive hemolytic Staphylococcus aureus, of bacteriophage pattern 52/52A/44A, was isolated from the father's nose. Two months later, after the boy had had several respiratory infections associated with asthma, new cultures were taken; the specimens from the noses of both father and son contained staphylococci which exhibited the bacteriophage pattern 55/52A/44A, identical to that originally obtained from the father.

By adherence to instructions on personal hygiene to prevent cross infection (it was common for the father to use his handkerchief on the boy's nose and for the child occasionally to sleep with the parents) the incidence of infections was reduced and the boy has had no asthma for two years despite incomplete investigation and lack of immunotherapy for allergy.

Case 2.—In this case of severe asthma, primarily due to a respiratory infection associated with conjunctivitis, a hemolytic staphylococcus which had been cultured from the mother's nose, throat, and eye had colonized the family and produced a variety of infections in most of its members.

A 6-year-old boy was seen on March 19, 1955, because of persistent asthma he had had since August, 1954, which had been controllable only by administration of cortisone, 100 mg. per day, given over a six-month period. To guard against superinfection, in view of the boy's frequent respiratory infections, the family physician prescribed also 300 mg. of tetracycline (Achromycin) daily during this period.

On examination, the boy showed typical moon facies due to excessive doses of cortisone (reduced dosage, when attempted, resulted in return of symptoms). No obvious signs of respiratory infection were noted, nor was there any evidence of asthma. However, a slight purulent discharge was visible in the inner canthus of the right eye, without any obvious conjunctivitis.

Laboratory examination showed a slight elevation in the number of leukocytes, without eosinophilia; a nasal smear was unrevealing. Roentgenographic studies of the chest showed an increase of the hilar markings, while those of the sinuses revealed a thickening of the mucosa of the right maxillary antrum, without evidence of any fluid.

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To improve the immunity of both the mother, who presumably was the carrier, and the patient, a vaccine was made of the staphylococcus obtained from the three members of the family, to which was added a stock-mixed catarrhal vaccine. Soon it was noted that minute doses of the vaccine resulted in exacerbations of the boy's asthma. The vaccine was therefore diluted further and the amount given increased cautiously.

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Case 3.—This case demontsrates the use of bacteriophage typing in the identification of a hemolytic staphylococcus which had colonized a family, three of whose members had asthma, and the transfer of the organism in the process of moving from one apartment to another. This case, described in detail elsewhere,[10] will be reviewed briefly.

A father and his two children, all with asthma in which infection was a factor, had been under observation; on culture, a hemolytic staphylococcus was obtained from them and from one other member of the family. Bacteriophage typing proved all the organisms to be identical, exhibiting the phage pattern 52A/79. The same organism ultimately was cultured from a kitchen plate during an investigation of the dissemination of the staphylococcus within the household. Simultaneously, the new and uninhabited apartment into which the family was moving was investigated, and no hemolytic staphylococci were encountered. Three months after habitation of the new apartment, agar plates were exposed again; the results revealed that the organism had now been transported into the new environment, staphylococci of the same bacteriophage pattern (52A/79) being isolated.

As in the earlier studies of intrafamilial contagion, an investigation was made of the father's six brothers and sisters and their children, as well as of his parents. Many members of the family were subject to frequent colds, sinusitis, bronchitis, asthma, boils, styes, and conjunctivitis. Of 13 cultures obtained from the 22 members of the family, 5 yielded coagulase-positive staphylococci which, however, on bacteriophage typing, differed from the one found in the members of the originally tested family. Bacteriological studies of this family continued over one year, during which time the staphylococcus type 52A/79 persisted in most members.

During one of these examinations, a nephew from the mother's side, who was helping with the children, was at once recognized as a former patient with asthma due to ragweed sensitivity and infection, who had been successfully treated and had remained asthma-free for the past five years. On culture, he yielded a hemolytic staphylococcus of type 52A/79. The investigation then was ext from

Table 2.—*Incidence of Hemolytic Staphylococci in Relation to Infectious Asthma in Colonized and Noncolonized Families*

Type of Family*	No. of Families	No. of Individual Members	No. of Persons Showing Hemolytic Staphylococcus	No. of Patients with Asthma	No. of Families with Asthma	Status of Patients with Asthma	
						Symptomatic	Asymptomatic
Colonized	12	42	36(85.7%)	11(26.2%)	8(66.8%)	9	2
Noncolonized	12	41	21(58.5%)	5(12.2%)	4(33.3%)	1	4

* Colonized families are those in which more than one member in the immediate family showed hemolytic staphylococci of identical bacteriophage pattern. The noncolonized families also showed hemolytic staphylococci, although to a lesser degree, but these were not identical when they occurred in more than one member in the family. At least one member showed a hemolytic staphylococcus, most often the patient.

to the mother's side of the family, but the identical staphylococcus was not obtained in any other member.

Case 4.—This case deals with a child with severe asthma and eczema, in whom, for seven years, a coagulase-positive hemolytic staphylococcus was repeatedly cultured from the nose, throat, eye, or skin. Continued use of a variety of antibiotics ultimately led to resistance to each one and to the emergence of a staphylococcus of type 80/81, which was also isolated from an infected ear of the mother. The asthma was further complicated by unusual pulmonary manifestations, presumably due to staphylococcic infection.

A female infant was first seen in December, 1951, at the age of 19 months, because of a generalized ezcema and asthma. From the beginning infection was considered a primary cause of her asthma. A coagulase-positive Staphylococcus aureus was repeatedly obtained from the nose and throat, at times in pure culture but frequently in association with streptococci.

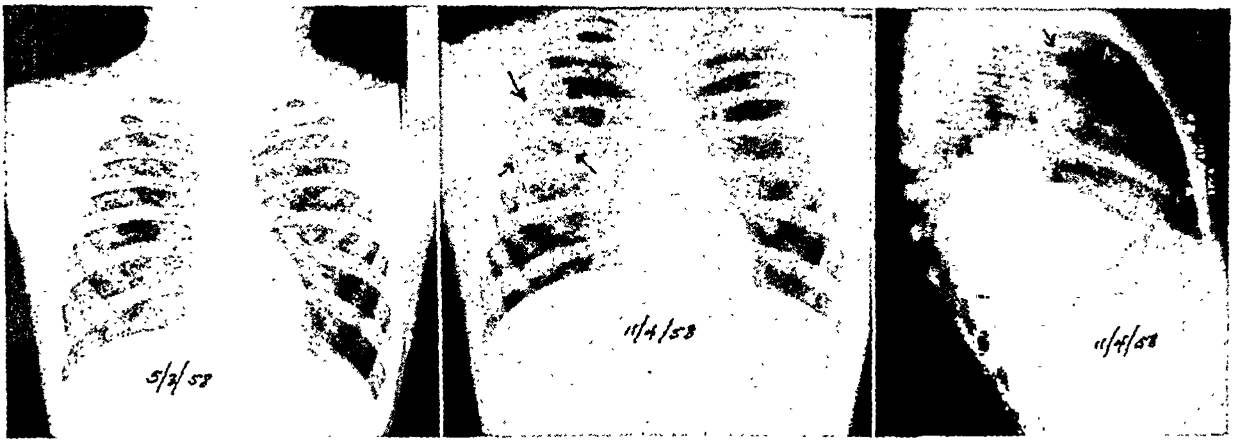

Fig. 1 (case 4).—Chest roentgenograms of asthmatic patient with staphylococcic infection. *Left,* routine chest roentgenogram, May 3, 1958, without abnormalities. *Center,* large emphysematous cyst in right upper pulmonary lobe. *Right,* lateral view of same (Nov. 4, 1958).

In 1955, the entire family was studied because of repeated infections both in the patient and in other members. Clinically, there was evidence of intrafamilial contagion. Bacteriophage typing, however, revealed that the staphylococci responsible for the symptoms were of unrelated types.

Because of the persistence of the infection in the patient, despite antibiotic therapy, the asthma continued to be moderately severe and cortisone was resorted to for therapy. A high degree of allergy was present in the patient, as shown first by passive transfer test and subsequently by direct testing as well as by clinical observation of sensitivity to many foods, pollens, and inhalants. The asthma became severe with each new upper respiratory infection and would improve for short periods only, with use of an antibiotic that was most often selected on the basis of sensitivity tests. Staphylococci were obtained from this child, at one time or

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another, from the nose and throat, the eczematous skin area, a purulent conjunctivitis, and a gluteal abscess.

In November, 1958, there was an unusual complaint of severe abdominal pain which had followed an acute upper respiratory infection with fever. The pain was, at times, so severe as to make the attending physician suspect an attack of gallbladder disease. The erythrocyte sedimentation rate (Wintrobe) was increased to 51 mm. per hour, and the white blood cell count was 24,000 per cubic millimeter, with an eosinophilia of 10%. The child was hospitalized for study.

Although the asthma was under control and there were no overt chest symptoms, an x-ray of the chest revealed a large emphysematous cyst in the right upper pulmonary lobe (fig. 1, *center, right*). Roentgenographic examination of the sinuses showed bilateral maxillary sinusitis (fig. 2, *right*). (Similar studies performed five months earlier had revealed no pathological findings [fig. 1, *left,* and 2, *left*]). Studies of cultures from the pharynx again revealed coagulase-positive hemolytic staphylococcus.

Subsequent follow-up studies show a gradual reduction in the cyst to approximately one-third of the original size. In March, 1959, there was a recurrence of the abdominal pain which again could not be accounted for clinically, and an x-ray of the chest once more revealed a small area of consolidation, this time in the left lower lobe (fig. 3). Pharyngeal culture again showed a hemolytic staphylococcus which, on bacteriophage typing, was revealed to be 80/81 and was completely unresponsive to any of the common antibiotics. (The bacteriophage typing pattern in 1954 had been 7/42E/42B/42D/44A and in 1955 39/44A.) New cultures were taken of all the members of the family, now increased to five, and this time hemolytic staphylococcus of the same type (80/81) was isolated from a draining infected ear of the mother.

In retrospect, the pulmonary findings were interpreted as being secondary to a staphylococcic infection of the lung which was probably not recognized because its symptoms were obscured by therapy with both steroids and antibiotics. It was of special interest that these infections occurred despite the continued use of an antibiotic of the tetracycline group, namely, glucosamine-potentiated tetracycline hydrochloride plus one part of oleandomycin (Cosa-Signemycin).

Comment

Although bacteriophage typing of staphylococci is a relatively new technique, it has already proved its usefulness in epidemiologic studies. It has been found helpful in tracing the dissemination of penicillin-resistant strains by hospital personnel, in food poisoning, and in epidemics of infantile diarrhea due to staphylococci.[3]

Since we had frequently found the ubiquitous hemolytic staphylococcus in studies of both individual persons and families who suffered from chronic or recurrent sinorespiratory infections, often associated with asthma, it was imperative to identify these organisms further to answer the questions raised in the introduction to this paper.

The data assembled here indicate that some families, particularly those in which asthma occurs frequently, are infected by specific hemolytic staphylococci. Other families, however, which presented the same clinical evidence suggestive of intrafamilial contagion showed no infection with hemolytic staphylococci and less asthma. The failure to demonstrate bacteriological colonization in families in which it was suspected clinically may have arisen from errors in the taking of a single culture, such as overgrowth by contaminants and failure to reach the site of infection. Other possible factors include the isolation of staphylococci which were not typable and which might have been identical had additional bacteriophages for typing been available. In some instances, by the time the staphylococci were transferred for bacteriophage typing, contamination had occurred. These failures can be resolved by study of a larger series of families, preferably in those in whom no antibiotic therapy has been used prior to bacteriological investigation.

Why some families become colonized by staphylococci is an intriguing question. Perhaps colonization results from a particularly active carrier, as in case 2, in which the mother had the staphylococcus in the nose, throat, and eye and dissemination, therefore, presumably was widespread. It is also possible that an allergic background may play some role. Suggestive evidence of this is presented by the correlation between asthma and the colonized families (table 2). Furthermore, experimental studies by myself and Dubos[4] indicate that prior sensitization of mice made them vulnerable to infection with the staphylococcus.

What is the significance of the higher incidence of asthma in the families colonized by pathogenic staphylococci? It is difficult to implicate the staphylococcus, even when hemolytic and coagulase-positive, since this organism is so frequently encountered in the nose and skin of persons in the general population without clinical disease. One cannot dismiss, however, the following observation previously reported: In a comparative study of seven related families in which asthma and pyogenic infections were frequently encountered, the hemolytic staphylococcus was encountered in 60% of the members.[1] On the other hand, control studies of 15 nonrelated families without asthma and relatively free from

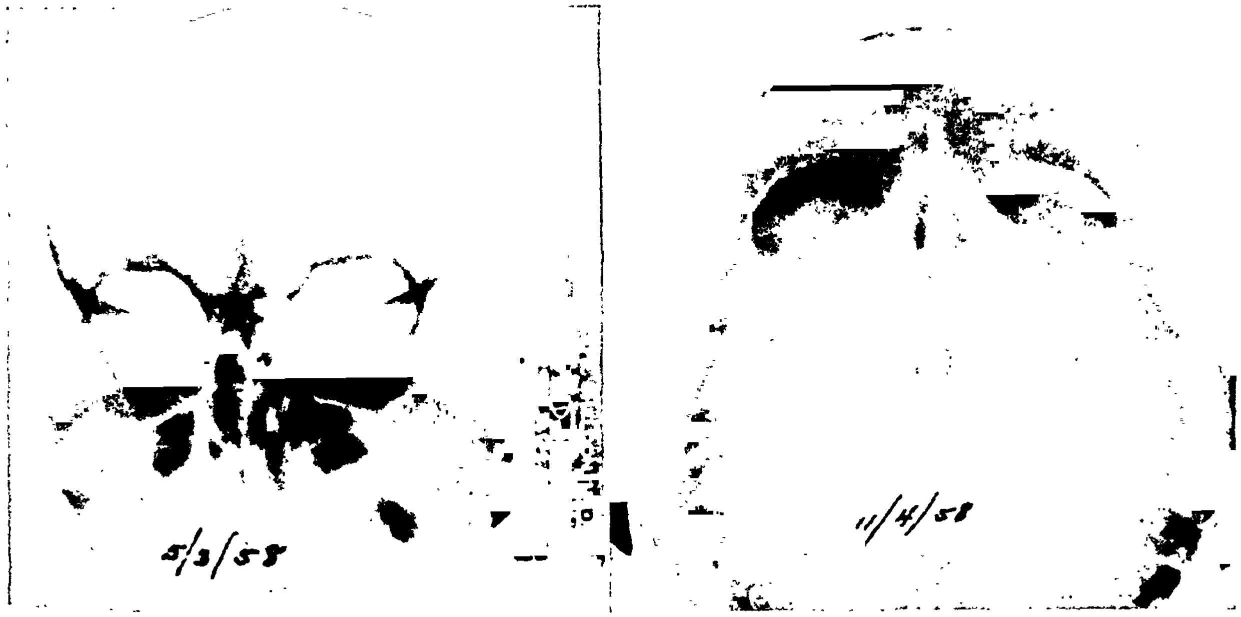

Fig. 2 (case 4).—Roentgenograms of sinuses. *Left*, May 3, 1958, normal. *Right*, Nov. 4, 1958, bilateral maxillary sinusitis.

respiratory infections yielded an incidence of staphylococci of only 16%. The percentage of streptococci, however, was the same in both groups (36%). Here too, further comparative study of a larger group of asthmatics and their families and an adequate number of control families is indicated.

What role, if any, does the hemolytic staphylococcus play in infectious asthma? The question cannot yet be answered definitively, since this micro-organism is so ubiquitous and may be a merely innocent bystander. We know,[1d] however, that this hardy organism can remain latent for long periods and then produce disease; that its toxin can enhance sensitivity and even produce autosensitivity[5]; and that its extract possesses pharmacological properties capable of producing smooth muscle contraction.[6] Although we cannot yet define the role of the hemolytic staphylococcus in asthma, we cannot dismiss it as an insignificant finding.

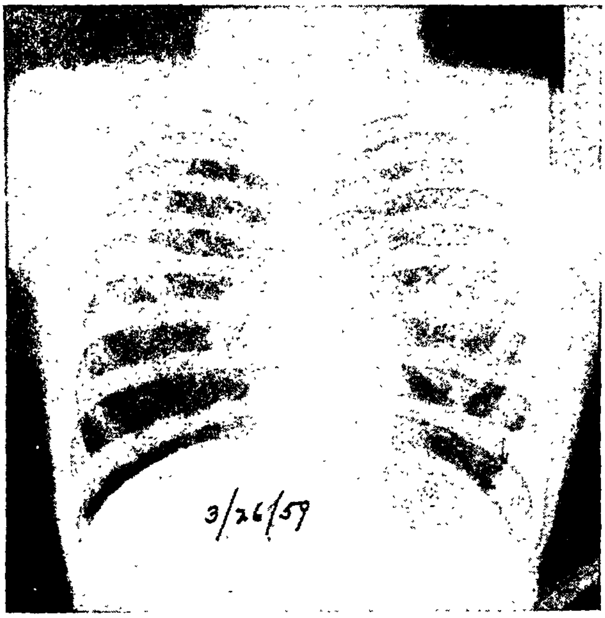

Fig. 3 (case 4).—Chest roentgenogram, April 26, 1959, small area of consolidation after marked reduction in emphysematous cyst in left lower lobe.

Assuming some ill-defined role for the staphylococcus in some cases of asthma, is a type-specific organism involved? The available evidence indicates that no one type of staphylococcus can be etiologically related to asthma. Although the staphylococcus of bacteriophage type 52A/79 was encountered most often, this was due to repeated study of the same family. Furthermore, the organisms encountered in these studies followed the general pattern of distribution of staphylococci in the population at large.

How does the staphylococcus colonize a family? One family study presented (case 3) indicates that, like most bacterial infections, the staphylococcus contaminates the environment so that infection may be transmitted not only by direct contact but indirectly as well by droplet or dust contamination. In case 3, it was shown that, as the family moved from a contaminated apartment into an uncontaminated one, contamination of the environment had occurred within three months or less. In this family the organism continued to be isolated from most members while they were under observation over one year.

This raises the question of the persistence of staphylococcic infection. Blair[7] had witnessed a case of recurring osteomyelitis in which a type-specific staphylococcus was encountered during three episodes of osteomyelitis over a 13-year period. The most persistent case studied in my series lasted only 18 months; moreover, a type-specific staphylococcus (previously isolated from the patient's husband) which had been present in the nose and eye of the patient for nine months, gave way to another type of staphylococcus which had only recently been recovered from the husband. He apparently was the carrier for the wife, and this helped to maintain in her a blepharitis of many years' duration. Here, too, continued study over several years would be helpful in determining the persistence of the staphylococcus, the mode of its transmission and its relation to the patient's asthma. That it plays some role in the asthma of this person is convincing, since the findings of skin tests with extracts of staphylococcus are positive and since she develops constitutional reactions from injections with staphylococcic vaccine. This is evidence of bacterial allergy, although it is possible that the staphylococcus may cause asthma for other reasons.

In view of the finding that contagion plays such an important role in recurrent or chronic sinorespiratory infections, with or without associated asthma, it is not enough to investigate the patient's allergies; it is also necessary to reduce infection by eliminating carriers, where possible, and by improving the patient's immunity.

Summary

Hemolytic staphylococci are frequently encountered in patients with recurrent or chronic sinorespiratory infections, with or without associated asthma. Bacteriophage typing of these coagulase-positive staphylococci indicates that some families with sinorespiratory problems become colonized with staphylococci. Persons in these families are more apt to have asthma. Other families in which clinically intrafamilial contagion seems to be a factor were not colonized; members of these had less asthma.

The distribution of staphylococci according to their reaction to bacteriophage typing was the same as that generally encountered in the population at large. No one type of staphylococcus could be etiologically related to infectious asthma.

Bacteriophage typing of staphylococci is of value in the epidemiologic study of chronic sinorespiratory infection and infectious asthma. It reveals foci of infections from which the respiratory tract may become reinfected, and it may reveal the presence of a carrier within the household.

55 Park Ave.

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MONITORING OF VENTILATION BY INTEGRATED DIAPHRAGMATIC ELECTROMYOGRAM

DETERMINATION OF CARBON DIOXIDE (CO_2) THRESHOLD IN ANESTHETIZED MAN

B. Raymond Fink, M.D., Edgar C. Hanks, M.D., Duncan A. Holaday, M.D.
and
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A direct determination of the threshold level of the respiratory center under conditions of anesthesia has been made, apparently for the first time, by use of the integrated diaphragmatic electromyogram (EMG). The disappearance of electrical activity of the diaphragm was used to determine the apneic carbon dioxide pressure (pCO_2) in anesthetized man. Controlled increases and decreases of ventilation in 11 anesthetized patients were correlated with the end-tidal carbon dioxide pressures. The onset of apnea occurred at an average pCO_2 of 38 mm. Hg, 10 mm. Hg below the mean level of unassisted respiration. Recovery from apnea occurred at an average pCO_2 that was 5 mm. Hg higher than at the onset. The discrepancy probably results from the slow equilibration of carbon dioxide between the blood and nerve cells of the respiratory center.

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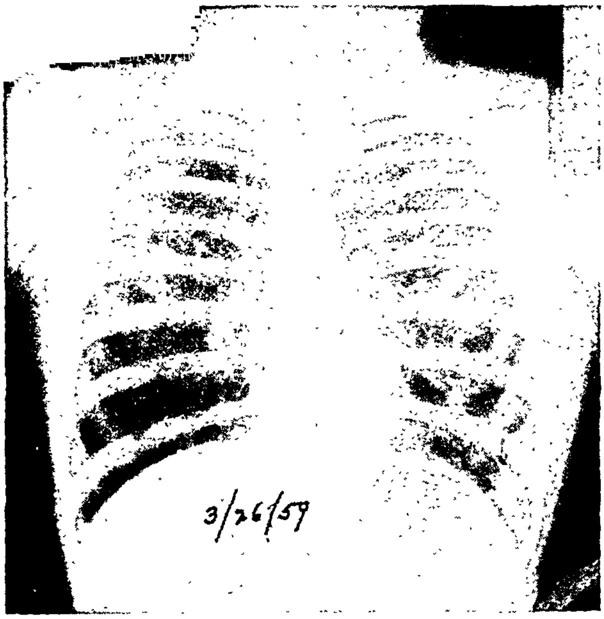

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Materials and Method

The subjects were 11 patients who were observed before or after minor operations and were anesthetized with a mixture of 70% nitrous oxide and 30% oxygen, and thiopental sodium, administered by intermittent or slow continuous intravenous injection. The patients breathed through a cuffed endotracheal tube and a nonreturn valve. Respiration was either unassisted or controlled by a ventilator whose frequency and tidal volume could be regulated independently. Inspiratory flow was recorded through a pneumotachograph and a Statham strain gauge (resistive transducer) and integrated electronically for volume measurements. The diaphragmatic EMG was obtained with insertion of two insulated monopolar needles, 5 mm. apart, through the left 8th, 9th, or 10th intercostal space respectively. The needles were advanced until a characteristic crescendo inspiratory discharge was heard in a monitoring loudspeaker. The EMG and the rectified EMG integral were recorded, together with inspiratory flow and volume, on a multichannel cathode ray oscillograph. The slopes of the integral, i. e., the average diaphragmatic activity, in successive breaths, were compared by returning the trace to the base line at the end of each inspiration (fig. 1). The endotracheal carbon dioxide concentration was recorded continuously with a Liston-Becker infrared carbon dioxide analyzer, which absorbs infrared energy in proportion to the carbon dioxide concentration of the sample.

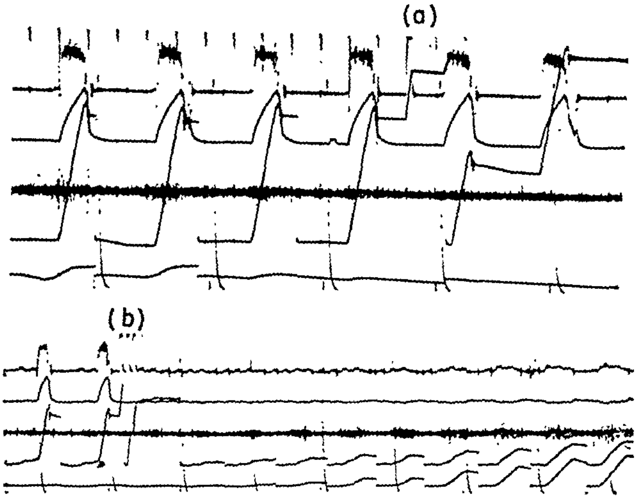

Fig. 1 (case 8).—Electromyographic monitoring of ventilation: (*a*) disappearance of diaphragmatic activity; (*b*) recovery of diaphragmatic activity during controlled ventilation. Traces from above down: time lines (seconds), inspiratory flow, airway pressure, diaphragmatic EMG, integral of inspiratory flow, integral of diaphragmatic EMG. Stroke volume of ventilator is observable in flow integral. At (*a*): large stroke volume, phasic activity in diaphragm became inaudible, end-tidal carbon dioxide tension (pCO_2) 42.5 mm. Hg (see fig. 2). At (*b*): after reduction of stroke volume and reappearance of phasic diaphragmatic activity at pCO_2 46.5 ventilator was turned off and patient breathed spontaneously and unassisted. Note parallel increase in diaphragmatic activity and inspiratory flow, observable in EMG and flow integrals. End-tidal pCO_2 rose to 51 mm. Hg and settled at 49 mm. Hg.

Procedure

The patients' unassisted respiration was observed for about 30 minutes to determine the existence of a stable minute volume and a stable end-tidal carbon dioxide tension (pCO_2). The patients were then connected to a mechanical ventilator which delivered a minute volume that approximated the spontaneous minute volume. Phasic diaphragmatic activity continued during this period, although not always synchronously with the inflation phase of the respirator. After five minutes, at this basal level of ventilation, the stroke volume of the ventilator was increased in steps of about 50 ml. The frequency of the ventilator remained constant. Each successive increase was accompanied by a decline in phasic diaphragmatic activity and a parallel fall of the end-tidal pCO_2. The pCO_2 at which phasic diaphragmatic activity disappeared altogether was noted (fig. 1 and 2). The stroke volume of the ventilator was then restored to the initial maintenance volume, and the pCO_2 at which phasic activity returned was observed. Finally, as soon as phasic diaphragmatic activity reappeared, the ventilator was turned off and respiratory exchange left to settle down at the level dictated by the patient's respiratory center.

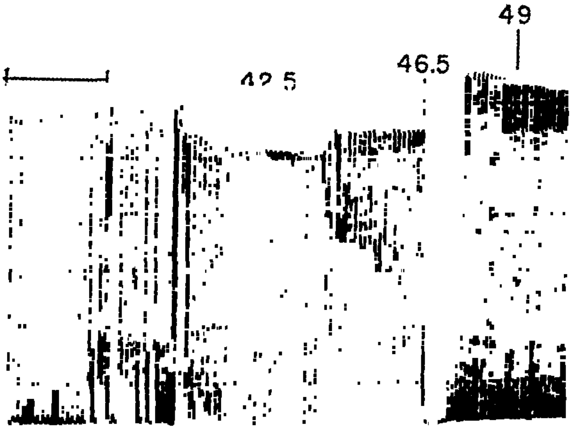

Fig. 2.—Infra red-analyzer record of expiratory CO_2 tensions. Same experiment as fig. 1. Top of each line represents end-expiratory value. Time mark at upper left: 1 minute. Numbers indicate end-expiratory CO_2 tension at time of disappearance (42.5) and of recovery (46.5) of phasic diaphragm activity, and pCO_2 level during unassisted spontaneous respiration (49).

Results

The results of 45 determinations in 11 consecutive studies are summarized in the table. Records from a typical experiment are presented in figures 1 and 2.

In the upper half of fig. 1 the patient was ventilated mechanically, with a stroke volume of 800 ml. at a frequency of 18 strokes per minute. The diaphragmatic EMG shows some continuous background activity and a burst of increased activity in phase with the inflation imposed by the ventilator. The inflation phase coincides with the period of positive pressure in the airway-pressure trace. In association with the high volume of ventilation, the diaphragmatic EMG shows decreasing activity with each successive stroke, as is evidenced quantitatively by the decline of the EMG integral of successive contractions. The signal at (*a*) marks the time at which phasic inspiratory increase of activity became inaudible. This point was regarded as the onset of apnea and was marked simultaneously on the carbon dioxide–analyzer record (fig. 2, at point 42.5).

The stroke volume of the ventilator was then reduced to 250 ml. at a frequency of 18 strokes per minute, and the return of phasic activity in the diaphragm was observed. In the bottom half of figure 1, point (*b*) shows the beginning of such a return, corresponding to the pCO_2 level marked 46.5 in figure 2. At (*b*) the ventilator was turned off and the patient allowed to breathe unassisted. The diaphragmatic activity increased slowly at first and then more rapidly, and there was a parallel increase in the inspiratory flow and tidal volume. In the carbon dioxide–analyzer record (fig. 2) there is a gap corresponding to the six breaths in which the inspiratory flow was very small. At this time, the carbon dioxide–analyzer sampled atmospheric air sucked in through the nonrebreathing valve, since little or no expired gas was flowing past the sampling site in the endotracheal tube.

End-Expiratory Carbon-Dioxide Tensions in Patients with Apnea During Nitrous Oxide-Thiopental Sodium Anesthesia

Case, No.	Resting Value of Spontaneous Ventilation, Mm. Hg	Cessation of Diaphragmatic Activity, Mm. Hg	Recovery of Diaphragmatic Activity, Mm. Hg
1	57.0	36.0	42.0
		40.5	44.0
2	53.5	45.5	51.5
		39.0	48.5
3	44.0	31.0	40.5
		34.0	42.5
4	56.5	44.0	48.5
		45.0	46.5
		41.5	43.5
	50.0	41.5	46.0
	51.0	44.0	48.0
5	44.0	37.5	41.5
		38.5	40.0
		37.0	39.5
	46.5	37.0	42.5
	46.0	37.0	40.0
6	48.0	40.0	45.0
	52.0	42.0	46.0
	50.0	37.5	42.0
	48.0	38.0	41.0
	50.0	38.5	42.5
7	45.0	36.5	43.5
	45.0	36.5	42.0
	40.0	33.0	36.0
	43.0	34.0	40.0
	46.0	36.0	44.0
8	51.0	40.0	44.5
	51.0	39.5	43.5
	59.0	42.5	46.5
	57.0	41.0	46.0
	58.5	40.5	45.0
9	51.5	38.0	40.0
	48.5	35.0	41.5
	47.5	36.0	42.0
	43.5	34.0	40.0
	44.0	35.5	40.0
	47.0	32.0	38.0
10	50.0	42.0	47.5
	48.5	42.5	46.5
		42.0	47.5
		42.0	49.0
		42.5	48.0
11	46.5	40.0	44.0
	47.5	39.0	43.5
	48.0	39.0	44.0
Mean	48.0	38.0	43.0
Standard error of mean (S. E. M.)	±1.2	±1.0	±1.1

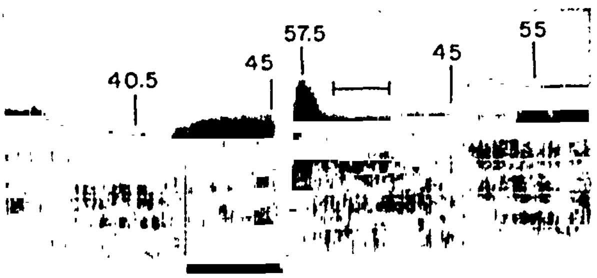

Fig. 3 (case 8).—End-tidal carbon dioxide (pCO_2) tensions in controlled apnea and recovery, 20 minutes after recording in fig. 2. Onset of apnea at 40.5 mm. Hg, recovery of phasic diaphragmatic activity at 45 mm. Hg. After turning off ventilator, indicated by gap signalling low expiratory volume, pCO_2 rose to 57.5 mm. Hg. Ventilator was then restarted at same stroke volume; pCO_2 returned to 45 mm. Hg, but vigorous phasic diaphragmatic activity continued. On turning off ventilator a second time (45), pCO_2 rapidly rose to 57.5 mm. Hg and settled to steady spontaneous ventilation level of 55 mm. Hg (time mark: 1 minute).

As alveolar carbon dioxide accumulated, the end-tidal pCO_2 rose to 51 and then settled down to a level of 49 mm. Hg. The overshoot is seen more clearly in another determination in the same patient, presented in figure 3. Here, apnea set in at a carbon dioxide tension of 40.5 mm. Hg, and recovery occurred at 45 mm. Hg, at which point the ventilator was turned off and the pCO_2 began to rise. In this experiment, the ventilator was turned on again at the peak of the carbon dioxide rise. The carbon dioxide tension was again depressed to 45 mm. Hg, but diaphragmatic contractions continued. Finally, the ventilator was turned off again, and the tension rose rapidly to the same level as the previous peak and then settled back to the equilibrium spontaneous-ventilation level of 55 mm. Hg.

It is evident from the data in the table that the recovery of diaphragmatic activity invariably occurred at a higher end-tidal pCO_2 than the onset of apnea. The difference ranged from 1.5 to 9.5 mm. Hg, with a mean of 5 mm. Hg (fig. 4). The pCO_2 at the onset of apnea averaged 38 mm. Hg, or 10 mm. Hg below the mean end-tidal pCO_2 maintained in spontaneous ventilation. When spontaneous ventilation resumed, there was a transient overshoot of 2 to 3 mm. Hg lasting one-half to one minute, sometimes followed by several smaller oscillations, after which the expiratory pCO_2 settled down to a steady resting level that averaged 48 mm. Hg.

Comment

These results establish, apparently for the first time in anesthetized patients, to what extent the end-expiratory carbon dioxide tension must be lowered to abolish spontaneous respiration and establish apnea. The reduction of 10 mm. Hg below the spontaneous ventilation level is surprisingly large in view of estimates of the so-called apnea point for unanesthetized man. Lindhard [1a] obtained this point by extrapolating backward the curve of ventilation volume during inhalation of carbon dioxide mixtures. The extrapolation indicated that the apnea alveolar carbon dioxide tension was about 2.5 mm. Hg below the spontaneous respiratory level. However, the ventilation-alveolar pCO_2 curves published by Eckenhoff and coauthors,[3] who used a more sensitive technique, indicate clearly that a linear extrapolation such as that made by Lindhard is invalid. Tenney [4] criticized the extrapolation on the ground that experimentally determined values were always higher than predicted. However, few such experimental determinations are available in the literature. Douglas and Haldane [5] determined the alveolar pCO_2 when the subject's breathing resumed after a two-minute apnea induced by voluntary hyperventilation. Recovery of respiration occurred at a tension of 37 mm. Hg, 3 mm. below his normal resting level of 40 mm. Hg. Nielsen's [1b] subject was hyperventilated and then paused until the urge to breathe returned, at which time an alveolar sample was obtained. The carbon dioxide tension in this sample was 41.5 mm. Hg, 1 mm. lower than the resting value.

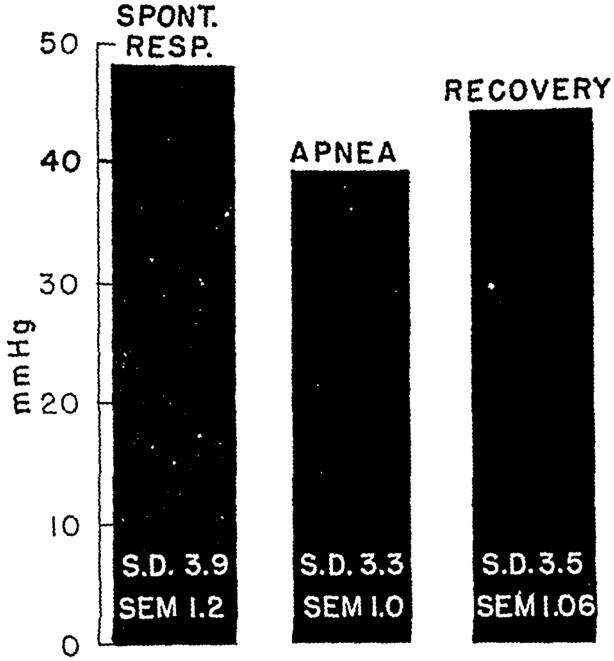

Fig. 4.—End-tidal carbon dioxide tensions (pCO_2) in anesthetised patients: bar graph of averages calculated from table 1. Spont. resp.: unassisted spontaneous respiration. S. D.: standard deviation. S. E. M.: standard error of mean.

The finding that the diaphragm does not recover immediately when the end-tidal pCO_2 rises above the apneic level was at first sight surprising. A difference between the apnea and recovery tensions was observed, regardless of whether hyperventilation was achieved by increased stroke frequency or by increased stroke volume of the ventilator. However, the discrepancy between the apnea and recovery tensions was smallest when the alveolar ventilation and the pCO_2 changed most slowly. Kety [6] suggested that the difference is due to slow equilibration between the carbon dioxide tensions in the blood and in the respiratory center. The true respiratory-center threshold to carbon dioxide must be intermediate between the "apnea" and "recovery" carbon dioxide tensions that were determined in these experiments. It also seems likely that the determinations by Douglas and Haldane [5] and by Nielsen,[1b] as well as Lindhard's [1a] extrapolation, do not represent the "apnea point" or respiratory center threshold but correspond to the "recovery" level of our own experiments. However, comparison with our data is limited by the fact that these were obtained during anesthesia and in the absence of such hypoxia as occurs in apnea after hyperventilation with air.

The overshoot of the end-expiratory carbon dioxide tension when spontaneous respirations was resumed is of some interest. It is believed that this reflects the circulatory time lag between the alveoli and the respiratory center. The reasoning on which this conclusion is based is represented diagrammatically in figure 5. As the tidal ventilation is progressively reduced, the pCO_2 in the blood climbs slowly to a level sufficient to stimulate the respiratory center and produce activity in the diaphragm. At this point (fig. 5, time line A) the ventilator is turned off. Since the stimulus to breathing is barely above threshold, the patient's breathing remains initially shallow. Therefore, when the ventilator is turned off the alveolar carbon dioxide tension rises rapidly, as seen in the carbon dioxide–analyzer

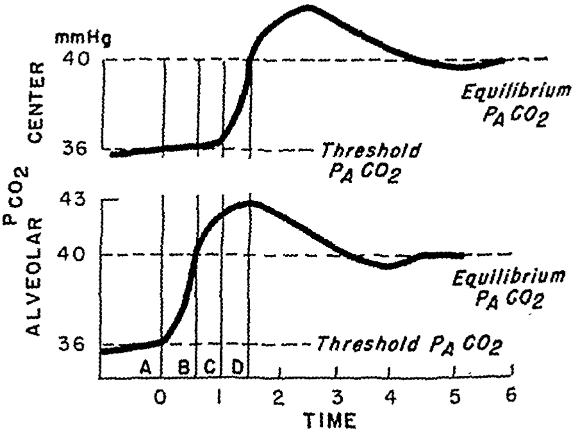

Fig. 5.—Diagrammatic analysis of alveolar and respiratory center carbon dioxide tensions during recovery from apnea.

curve of figure 3. However, at the respiratory center the rapid rise in pCO_2 begins later than at the alveoli (fig. 5, time line C), the lag being equal to the lung-brain circulation time. Similarly, when the carbon dioxide equilibrium tension is reached in the alveoli (time B), this tension has not yet been reached in the center. The patient, therefore, continues to have hypoventilation and the alveolar pCO_2 climbs above equilibrium level. When this above-equilibrium concentration reaches the center, the patient begins to have hyperventilation and the alveolar tension begins to drop. The interval B-D from the alveolar pCO_2 rise above equilibrium level to the peak-alveolar pCO_2—between 7 and 11 seconds in these studies—represents the lung-medulla circulation time. The presence of smaller oscillations after the first large overswing (fig. 3) is readily explained on the same basis.

Continuous low-grade "background" activity was observed in the diaphragm at the onset of apnea and continued for one or more minutes thereafter. This background activity was found in all cases and invariably disappeared if the pCO_2 fell more than 2 mm. Hg below the apneic tension. Recovery of phasic activity was preceded by return of the continuous discharge. The presence of background activity in the diaphragm is in agreement with the observations of Nieporent.[7]

Summary

The integrated diaphragmatic electromyogram (EMG) gives a measure of the inspiratory activity of the respiratory center. Disappearance and recovery of diaphragmatic activity, produced by controlled increases and decreases of ventilation in 11 anesthetized patients, were correlated with the end-tidal carbon dioxide pressures (tensions) (pCO_2). The onset of apnea occurred at an average pCO_2 of 38 mm. Hg, 10 mm. Hg below the mean level of unassisted respiration. Recovery from apnea occurred at an average pCO_2 that was 5 mm. Hg higher than the onset. The discrepancy probably results from slow equilibration of carbon dioxide between the blood and nerve cells of the respiratory center.

622 W. 168th St. (32) (Dr. Fink).

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THE TRANSMISSION OF HATRED.—Thorne has charted the "epidemiology of hostility" through family studies. Thorne has pointed out the contagious quality of hostility, its tendency toward chain reactions, and its extreme potency when the recipient is in an inescapable position. The application of his thesis to institutions is apparent and appears borne out by the present observations of a penal institution. The sentries, our youngest siblings of the brig family, feel subject to inescapable frustration and hostility. The sentry is often young, inexperienced, lacks mature outlets, and is hard pressed to deal with his "chronic anger state." Standards within his peer group sanction downward acting-out, and he readily translates pressures from his superiors as well as neurotic hostility into aggression toward the prisoners. Of course, the cycle does not end there. Although severely restricted, the prisoners retaliate with negativism, accidents, sluggishness, and malingering. A further result, pointed out by Thorne, is the build up of mutually suspicious and paranoid attitudes. Although not striking in the present study, marked paranoid attitudes on the part of prison personnel have been described in other studies. Thorne's epidemiologic framework is a useful approach to the subject. An interesting sidelight in the epidemiology of hostility is the practice of mass punishment in the brig. Implicit in this device is the wish that the group will become enraged and turn on the one, enforcing the discipline of the authority. Thus, mass punishment is the planned use of the retaliation motif to maintain control.—Lieut. L. D. Hankoff, M.C., U.S.N.R., Interaction Patterns Among Military Prison Personnel, *United States Armed Forces Medical Journal,* December, 1959.

EFFECT OF DEXTRO PROPOXYPHENE, MEPERIDINE, AND CODEINE ON POSTOPERATIVE PAIN

William S. Van Bergen, M.D., William C. North, M.D., Ph.D.
and
Mary Karp, M.D., Chicago

An investigation to determine the comparative value of pain-relieving drugs conducted on 94 private patients who had undergone orthopedic surgery was started 48 hours postoperatively and continued for three days. Four substances were used: dextro propoxyphene hydrochloride, 100 mg.; codeine phosphate, 65 mg.; meperidine hydrochloride, 100 mg.; and placebo. Capsules were administered at four-hour intervals. Intensity of pain was scored and interrogation of patients was done by a physician. The drugs were found to be significantly more pain-relieving than was the placebo. The analgesic effectiveness of the drugs in the doses used was indistinguishable. The over-all analgesic effectiveness of drugs and placebo was similar to that found by other workers. A separate study on placebo effect showed that the patients discriminated more accurately between analgesics and placebos on the first day of study than on subsequent days.

The management of postoperative pain is generally based on a "clinical impression" that, immediately after performance of an operation, there is severe pain, which gradually wanes until the fourth to sixth postoperative day when it ceases. On the basis of this assumption, medication is ordered: first, potent narcotic analgesics are given by injection in the immediate postoperative period; next, less potent narcotics are used; and, finally, non-narcotic analgesics of the salicylate type are given.

Several analyses of the severity of postoperative pain have appeared in the literature; the results have been conflicting. Papper and associates[1] reported that 38% of 110 patients did not complain of pain in the 24-hour period after operation. Jaggard and associates[2] studied 1,005 patients and found that only 64% required narcotic analgesics after having undergone various types of surgery. On the other hand, our experience with private patients indicates that only 6.6% of 167 patients who had undergone various orthopedic operations did not require potent analgesic medication, and 10% of 100 patients who had had rectal surgery did not have sufficient pain to warrant the postoperative administration of a narcotic. Of 100 patients undergoing thoracotomy, 7 required no narcotic throughout the postoperative period and 17 required none in the first 24 hours.

A number of objections may be raised to this means of determining the existence of pain, and they probably account for the discrepancy in the results. However, the curves in the figure were constructed from data of this type that are available for analysis, relating the intensity of pain, expressed as the average number of doses of a narcotic administered per patient, to the length of time after surgery. It will be noted that, although the number of doses of any one drug given on any postoperative day varied with the type of surgical procedure performed, the rate of decline was similar.

The use of narcotic drugs is fraught with the possibilities of addiction or sufficient central nervous system depression to retard the rate of recovery from the trauma of surgery, or both. The development of a new analgesic, dextro propoxyphene hydrochloride (Darvon), which was claimed to be about equivalent in effectiveness to meperidine (Demerol) hydrochloride or codeine but to be devoid of addictive liability and central nervous system depression if given in analgesic doses, suggested the possibility that adequate relief of pain might be accomplished more safely than was possible previously. To that end, the study reported below was undertaken.

Materials and Method

Ninety-four private patients who had undergone various types of orthopedic operations served as subjects. The only selective requirement was that the patients chosen were likely to be in the hospital for at least five postoperative days. They were housed on the same floor and cared for by the same group of nurses. The distribution of patients with respect to areas of surgical procedure is given in table 1.

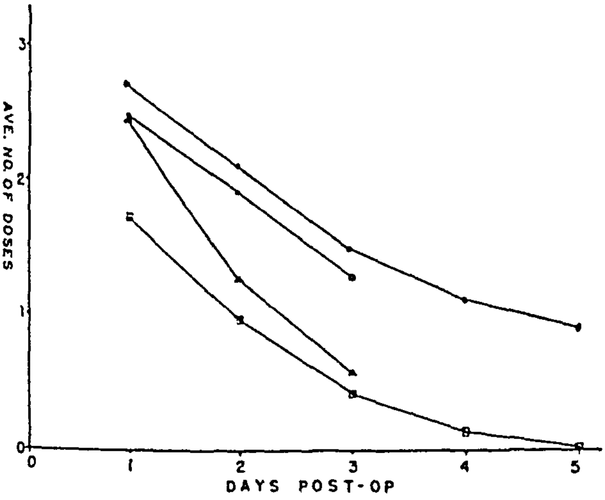
Four medicaments were used: dextro propoxyphene hydrochloride, 100 mg.; codeine phosphate, 65 mg.; meperidine hydrochloride, 100 mg.; and placebo.

From the Department of Pharmacology, Northwestern University Medical School, and the Department of Anesthesiology, Chicago Wesley Memorial Hospital.

Read before the Section on Anesthesiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 12, 1959.

The experiment was started 48 hours postoperatively and continued for three days, if possible. No other analgesics were given. All medicaments were given orally in identical capsules. The capsules were individually packaged and coded so that neither the observers, nurses, nor patients knew the identity of individual medicaments. The capsules were given by the nurses every four hours on a 2-6-10-o'clock schedule. The order of administration was systematically randomized. All patients received all four medicaments, with the exception of 20 who did not receive the placebo. The 2 a. m.-capsule was given if asked for by the patient, but observations on the effect on pain with this dose were not included in the results.

The patients were questioned three or four times per day about premedication pain, postmedication pain, duration of relief obtained, and side-effects experienced during each four-hour period. The pain was scored as follows: 1 = no pain; 2 = mild pain; 3 = moderate pain; and 4 = severe pain.



Incidence of postoperative administration of narotics: solid circles, orthopedic surgery; open circles, thoracic surgery; triangles, abdominal surgery (Keats[44]); open squares, rectal surgery.

No attempt was made to determine hourly pain scores. The interrogation of all patients was carried out by a physician. Observations were recorded numerically on a special chart, together with the code number of the drug.

Relief from pain is defined as the difference between the predrug score and the lowest score reported in the four hours after taking a capsule. The mean pain-relief scores were determined for each medicament on each postoperative day. The percentage of administrations of each drug giving relief was also determined. The degree of relief afforded by only the first dose given each patient was evaluated. Data concerning constant reactors, inconstant reactors, and constant nonreactors to placebo were separated and analyzed. Only those patients who had received two or more doses of placebo while they had pain were included in these groups.

Results

All patients were caucasoid. Thirty-eight (40.4%) were men and 56 (59.6%) were women. The mean age was 45.3 ± 1.9 years. Sixty-three (67%) of the patients completed the entire three-day study.

TABLE 1.—*Orthopedic Operations by Location in Ninety-four Patients Given Postoperative Analgesics*

	Operations Performed	
Location of Operation	No.	%
Foot	19	20.2
Ankle	2	2.1
Lower leg	3	3.2
Knee	10	10.7
Femur and hip	25	26.6
Back	13	13.8
Shoulder	10	10.7
Humerus	4	4.3
Forearm	4	4.3
Hand	4	4.3
Total	94	100(+)

Thirty-two per cent of the patients had severe pain (grade four) sometime during the study, and only 7.5% reported no pain at any time during the study. Of the 1,132 medicaments administered (about 300 doses of each), 68% were given at times when definite pain was present, namely, of 229 placebo capsules, 71.6% (164); of 305 codeine capsules, 67.3% (205); of 302 dextro propoxyphene capsules, 70.2% (212); and of 296 meperidine capsules, 63.5% (188).

Only the 769 administrations of the four medicaments which were given while pain was present were used to analyze pain-relief scores (table 2). Relief afforded by the active agents was significantly greater than that afforded by placebo on the first day and for the three-day period.

Meperidine and dextro propoxyphene significantly lowered the mean pain score on postoperative day number four, but there was no difference between the effects of any of the agents on the last day of the study. None of the active agents differed significantly from each other. A progressive daily decline in relief was provided by all agents except placebo.

TABLE 2.—*Mean Pain Relief Scores Obtained from Four Drugs Given Postoperatively*

	Drug Given				
Postoperative Day	Placebo	Codeine	Dextro Propoxyphene	Meperidine	Total
3*	0.43	0.76†	0.79†	0.95†	0.75
4	0.34	0.58	0.76†	0.71†	0.62
5	0.49	0.60	0.49	0.44	0.51
Total	0.41	0.67†	0.72†	0.77†	0.66

* Postoperative day 3 includes time between 48 and 72 hours after completion of surgery.
† $P = < 0.01$ compared with placebo responses.

The enumerative data on the medicaments whose administration gave relief are as follows: Pain was relieved to some extent about 42% of the time by placebo and about 58% of the time by the active agents, namely, 56.5% of the time by codeine, 60.5% of the time by dextro propoxyphene, and 65.4% of the time by meperidine ($p<0.01$ compared with placebo response).

TABLE 3.—*Pain Relief Scores with Use of Only First Dose of Four Medicaments Given*

Drug Given		Relief of Pain	
Type	Doses, No.	Mean Score	%
Placebo	14	0.57	57
Codeine	21	0.85	62
D-Propoxyphene	30	0.97	73
Meperidine	18	1.00*	83

* P = <0.05 compared with placebo response.

There were no differences in the duration of relief afforded by any of the capsules including placebo, the mean duration in hours having been, respectively, 3.26 for placebo, 3.28 for codeine, 3.17 for dextro propoxyphene, and 3.20 for meperidine. The maximum possible duration of relief was four hours, because another medicament was given at that time.

The responses to and the first dose of the medicaments administered are summarized in table 3. The results give a wide spread, but, because of the small size of the sample, these data are not significant.

The number of patients reporting various side-effects from any of the four medicaments is given in table 4. Drowsiness was the most frequently reported side-effect. The total reported side-effects from use of placebo and dextro propoxyphene were considerably lower than those reported from meperidine and codeine.

A summary of placebo effects is given in table 5. The placebo reactors had less pain and got more relief from all medicaments administered than did the other patients.

TABLE 4.—*Incidence of Side-Effects with Use of Four Medicaments*

	Medicament Given				
Side-Effect	Placebo	Codeine	Dextro Propoxyphene	Meperidine	Total
Vertigo	1	3	...	2	6
Nausea	3	7	2	5	17
Emesis	1	1	...	1	3
Excitation	...	...	...	1	1
Drowsiness	1	8	8	9	26
Headache	2	3	2	2	9
Gastric distress	2	5	1	3	11
Total	10	27	13	23	73
Total doses administered	229	305	302	296	1,132

Comment

The results reported here are in agreement with the work of others.[3] That is, about 40% of the time administration of a placebo was followed by a reduction in the severity of pain. Administration of any one of the analgesic drugs resulted in a decrease in pain in a significantly larger percentage of the patients, although none of the agents could be distinguished from another. No agent provided relief all the time.

From the figure it can be seen that 48 hours after operation there is still pain severe enough to require the use of frequent doses of narcotic agents. Orthopedic patients, particularly, seem to require more frequent doses of narcotics.[4] The incidence of administration of narcotics is not a quantitative measure of severity of pain but reflects the frequency with which pain occurs.

Oral administration of narcotics does not provide dependable analgesia comparable to that obtained by injection of the same agent.[3a] However, meperidine and codeine are absorbed from the intestine in quantities sufficient to provide analgesic blood levels.[5] Oral medication has obvious advantages from the standpoint of nursing care. In the period studied here, the orally given medicaments were therapeutically effective.

TABLE 5.—*Analysis of Postoperative Placebo Effect in Fifty-three Patients*

	Type of Response		
	Constant Reactors	Constant Nonreactors	Inconstant Reactors
Number	12	20	21
Sex			
Male	4	10	10
Female	8	10	11
Mean Age, Yr.	50	42	41
% reporting placebo side-effects	17	10	19
% of time pain present	70	83	80
Mean pain score before use of drugs	2.16	2.34	2.19
% relieved by use of placebos	100	...	42.4
% relieved by use of analgesics	74.5	40.6	61.8

This study was primarily one of relief of pain. The technique of grading pain intensity numerically and measuring relief thereby is, in actual practice, difficult and insensitive; yet with this crude device significant drug effects could be demonstrated on the first and second days of the study and for the entire three-day period (table 3). The failure to detect drug effects on the third day might result from the existence of less severe pain, so that the placebo effect became more important in providing relief.

For that reason we were interested in examining the patients with respect to their reaction to placebos (table 5). Surprisingly, the so-called placebo reactors, that is, those patients who always obtained relief from pain when given a placebo, had significantly less frequent pain than the others. The active analgesics relieved pain in a significantly higher percentage of administrations to the placebo reactors than to the nonreactors. The patients discriminated between the effect of placebos and analgesics best on the first day of the study when the pain was most severe, and this ability to identify the placebos waned as the pain declined. This agrees with the findings of Free and Peeters[6] and is contrary to the results reported by the Harvard group.[3c]

Evaluation of the duration of analgesia is difficult in a situation in which pain is intermittent. No data are available to indicate the natural course of postoperative pain. The values obtained for duration of pain relief are not significantly different and reflect two disadvantages of this study if used to determine the duration of the analgesic effect of medicaments—namely, no value can be greater than four hours, and apparent analgesic duration may merely be a reflection of the absence of a painful stimulus.

Free and Peeters[6] reported that analgesic effectiveness in postoperative pain could be most readily evaluated by means of the first postoperative dose of an analgesic. Analysis of our results failed to demonstrate a significant difference between any one analgesic and the placebo in ability to relieve pain, measured by either pain score or incidence of relief (table 3); this may be a reflection of the necessarily small number of doses administered. With use of the results of all administrations of medicaments on the first day of this study, the differences between any one analgesic and the placebo were highly significant.

The benefit of the experimental design used here to evaluate the side-effects of the drugs administered is limited. Only those untoward reactions which would be expected to occur promptly after administration could be attributed to the drugs used. Furthermore, postoperatively, patients have many disturbances in their physiology which need not be related to analgesic therapy. The over-all incidence of side-effects of the medicaments used (table 5) is low and corroborates more meaningful data on these drugs already reported in the literature.[7]

Summary

Postoperative pain is a variable entity and difficult to assess. In the 94 postoperative orthopedic patients studied here, 92.5% had pain of at least moderate severity sometime in the three-day period beginning 48 hours after the end of operation. In these patients, orally administered dextro propoxyphene (Darvon) hydrochloride, meperidine (Demerol) hydrochloride, and codeine were significantly more effective than a placebo in relieving pain. The over-all response to the medicaments given, active or placebo, was similar to that found by other workers. Oral medication with moderately potent analgesics is effective in relieving pain in this period and probably interferes less with the physiological processes of the body than do more potent narcotics. The analgesic effectiveness of dextro propoxyphene, meperidine, and codeine, in the doses used, was indistinguishable.

250 E. Superior St. (11) (Dr. Karp).

This study was supported, in part, by a grant in aid from Eli Lilly & Company, Indianapolis 6.

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RETURN TO WORK AFTER SURGERY.—I make one plea to surgeons. When you are satisfied concerning the surgical recovery of a patient, leave the decision as to return to work to the plant physician, if the patient's company has one. A well-trained and experienced industrial physician knows the nature of the employee's job and is better able to judge whether the employee should go back to full-time, or part-time work, or be assigned temporarily to another job. The addition of another two-week period of convalescence merely for the sake of safety can often be avoided by so doing.—A. J. Fleming, M.D., Return to Work After Surgery—An Industrial Study, *Journal of Occupational Medicine,* October, 1959.

ACUTE GASTRIC DILATATION

Ted F. Leigh, M.D., Atlanta, Ga.

In cases of acute gastric dilatation the progression of symptoms is rapid and prompt relief is necessary. Since the pathogenesis of the condition is poorly understood, however, treatment is still empirical. The most effective measure is to intubate the stomach and to remove the accumulated secretions and gases by continuous suction. Dilatation of the stomach has frequently followed abdominal surgery in the past, but three case histories here presented show that it sometimes follows other trauma, especially in patients immobilized for various reasons. In the fourth case, that of a 69-year-old woman, no obvious cause was found, but the condition progressed rapidly to a fatal termination. Acute dilatation of the stomach is a serious condition that is easily diagnosed and should be treated promptly.

Acute gastric dilatation is a condition characterized by clinical findings of vomiting, abdominal distention, and collapse. Radiographically, it is characterized by the identification on abdominal films of a large gastric shadow whose contents are air and fluid in varying proportions. The importance of a radiographic examination in suspected cases of gastric dilatation rests in the fact that the diagnosis can be quickly established by proper examinations of the abdomen and the condition can be differentiated from a host of others which show the same clinical features of vomiting, distention, and collapse. These other conditions include generalized dilatation of the large or small intestine caused by obstruction; localized dilatation of these same structures, as in volvulus of the small intestine, the cecum, or sigmoid; ascites; pneumoperitoneum; cyst or tumor; and distention of the urinary bladder.

Pathogenesis

The pathogenesis of acute gastric dilatation is of interest and in its consideration the following factors must be taken into account: (1) etiology of the gastric dilatation, (2) origin of the fluid contained within the stomach and duodenum, (3) origin of the air in the distended stomach (and duodenum), and (4) causative factors in the associated gastric or duodenal obstruction which is sometimes present.

Cause of Gastric Dilatation.—The most widely accepted theory of acute gastric dilatation is that it is caused by paralysis of the stomach, which has been described as being analogous to intestinal paralysis, such as occurs with peritonitis. Dragstedt and others [1] attribute this paralysis to a reflex inhibition of the peripheral gastric motor mechanism through efferent impulses which reach the stomach by way of the vagi and splanchnics. Their experimental evidence is adequate to show that the stimulation of either visceral or somatic central nerves may produce such reflex gastric inhibition, allowing the stomach to distend abnormally as fluid and air are progressively accumulated within it. These authors also believe that the principal contributing cause of death in these cases is failure of reabsorption of the gastric and pancreatic juices and more particularly of the inorganic elements, sodium and chloride, within these juices.

Origin of Fluid Contained Within the Stomach.—The fluid in the stomach is derived from several sources—gastric juice secreted by the stomach wall; pancreatic juice, bile, and secretions of the duodenal mucosa which reflux into the stomach; ingested material, including both fluids and food; and secretions, notably saliva, derived from the alimentary tract proximal to the stomach.

Origin of Air in the Distended Stomach.—It is generally agreed that all air seen in the stomach during acute gastric dilatation is derived from outside the body.[2] Morris and others [2c] after experimenting on animals and human beings, reached the conclusion that the air which is present in the stomach in acute gastric dilatation comes from sucking air or swallowing air. They state, "What keeps everyone from sucking air is the resistance offered by the superior esophageal sphincter, and one might postulate that general debilitation, anesthesia, or some reflex may decrease the tone of this structure, and allow significant volumes of air to enter the upper part of the gastro-intestinal tract."

Cause of Obstruction.—There are several factors which may contribute toward an associated obstruction in the distal end of the stomach or duodenum. It is postulated that an enlarging stomach in itself may so angulate the distal end of the stomach or proximal duodenum that obstruction results. In many instances, the enlarging stomach displaces much of the small intestine into the pelvic area, putting such traction on the mesentery and mesenteric vessels that they compress the transverse part of the duodenal loop against the lumbar vertebra,

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From the Department of Radiology, Emory University School of Medicine.

Chairman's address, read before the Section on Radiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

which results in a partial or complete midline obstruction. In the presence of a body cast, there is sufficient hyperextension of the spine and reduced mobility of the abdominal musculature to cause a similar obstruction by the mesentery and mesenteric vessels in the transverse arm of the duodenum.[3]

Clinical Findings

The clinical features of acute gastric dilatation are classic. The chief symptoms are vomiting, abdominal distention, and collapse. Lesser symptoms include pain over the stomach, insufferable thirst, and scanty urine. The vomiting occurs at short intervals and once begun becomes the most prominent feature. It is not as debilitating as it would seem and does not give the patient a feeling of relief. The vomitus is usually thin watery material and is small in amount compared to the total fluid present in the stomach.

The degree of abdominal distention is varied, depending to a large extent on the size and shape of the abdomen and the degree of gastric distention in the individual case. More than likely the gastric distention causes the epigastric and periumbilical pain which is often present. Before complete gastric paralysis develops, there may be visible peristalsis on the abdominal wall.

The stomach fluid in the earlier stages is yellow or green and odorless. Later it becomes brown or black because of admixture with blood, usually contains biles, and has an offensive odor. The fluid volume varies from one to several liters. In one reported case, the stomach was estimated to contain 7,500 cc. of fluid; in another case, the distention was so great that the body could not be placed in a casket. Esophageal obstruction is sometimes present and is due to a deformity at the cardia initiated by the enlarging stomach.[23] The development of acute gastric dilatation can be exceedingly rapid. Within 24 to 48 hours, a normal stomach can expand into a cyanotic and hyperemic sac, filling almost the entire abdomen and extending caudad to reach the pelvic floor.

The treatment for acute gastric dilatation is not entirely satisfactory. In postoperative cases, dilatation may be prevented by suction applied to a stomach tube. Operative results for the dilatation itself have been discouraging. The principal types of procedures which have been performed include gastroenterostomy, gastrostomy, gastrotomy, and gastrectomy. The poor results of surgery are attributed to the condition of the patient and to the severe irreversible damage in the gastric wall.

Radiographic Characteristics

In the diagnosis of acute gastric dilatation, radiographic examination can be of help in establishing the diagnosis and in differentiating it from other conditions. An examination of the abdomen, made with the patient in recumbent position, will usually reveal the stomach as a large mass filling the upper and middle part of the abdomen and displacing the intestines laterally and caudad. When the stomach lumen contains large amounts of fluid and only small amounts of air, the gastric shadow may be poorly defined because it is of the same density as the surrounding abdominal structures. Air in the gastric lumen, on the other hand, is easily recognizable. When present in relatively small quantities, it is seen as a translucent shadow superimposed on the fluid (fig. 1*A*). In larger quantities, it may actually outline the stomach itself (fig. 2). Air may also outline the duodenum if sufficient amounts are located in that area.

An examination made with the patient in upright position will show an air-fluid level in the left upper quadrant of the abdomen, with the air mass corresponding to the contour of the fundus of the stomach and located immediately beneath the left diaphragm leaf (fig. 3*A*). In addition, a second air-fluid level is sometimes seen in the right middle or upper part of the abdomen, situated more caudad than the one on the left and shorter in length (fig. 3*C*); this level is due to the presence of small amounts of air trapped in the prepyloric region of the stomach or in the duodenal cap. Again the fluid in the stomach appears as a homogeneous shadow in the middle part of the abdomen but may be difficult to identify because of its density in relation to the surrounding structures (fig. 3*C*).

Other types of abdominal films can be made to aid in the diagnosis of acute gastric dilatation, particularly if the patient's condition is such that a film of the patient in an upright position is contraindicated; these include left and right lateral decubitus films and transabdominal films. These, in all instances, will show air fluid levels, with the air pocket outlining the portion of the distended stomach in which it is located.

Abdominal examinations after the oral administration of contrast medium may at times be indicated, particularly for delineating the size of the stomach (fig. 3*C*), and for determining the patency of the lower part of the esophagus at the cardia (fig. 1*B* and 4*B*). In these cases, the water soluble mediums are to be preferred over barium sulfate mixtures and iodized oils.

Predisposing Factors

There are certain predisposing factors in the development of acute gastric dilatation. These can be divided into surgical procedures in the abdomen, acute illness or convalescence, chronic illness, disorder or deformity of the spine, overloading of the stomach, abdominal trauma and intra-abdominal accidents, confinement, and vagotomy, induced either surgically or medically. To these may be-added those cases of acute gastric dilatation in which there is no obvious cause; these might be classed as idiopathic cases, although it is probable that a predisposing factor exists which defies detection.

Dilatation attributed to overloading of the stomach is of particular interest. In a report by Markowski[4] four cases of acute gastric dilatation attributed to overloading the stomach with food are cited. All patients were prisoners-of-war and were emaciated. Two of these patients developed the dilatation although they had eaten a meal no larger than one eaten by a normal healthy person. The author postulated that the acute dilatation was superimposed on a chronic one caused by malnutrition and that the sudden intake of food caused paralysis of an already weakened wall. He stated that chronic dilatation of the stomach, due to the prolonged intake of large amounts of food of poor caloric intake, was so common that they used to call it the occupational disease of the prisoners-of-war.

The following cases will serve to illustrate some of the clinical and radiographic characteristics in this entity of acute gastric dilatation.

Report of Cases

Case 1.—A 43-year-old woman had a long history of urinary calculi. A cystoscopy was performed on Sept. 15, 1955, with removal of calculi from the left ureter. An indwelling catheter was placed in the lower half of the left ureter. On this same day laboratory examinations disclosed an imbalance of the electrolytes. On the next day, because of abdominal distention, a radiographic examination of the abdomen was carried out (fig. 2), which disclosed an acute gastric and duodenal dilatation with a predominant amount of air. The dilatation was relieved by intubation and suction. After tl there was no further distention. About this san time the electrolyte disturbance had been correcte

Case 2.—A 17-year-old man was admitted to tl hospital in an unconscious state, having sustaine a simple fracture of the right femur in an aut mobile accident. He was initially placed in tractio but two weeks later, because of a disturbed ment state, he was placed in a plaster hip spica. H mental state cleared slowly, and he was discharge from the hospital. Seven weeks later persister vomiting developed and he was readmitted. Afte

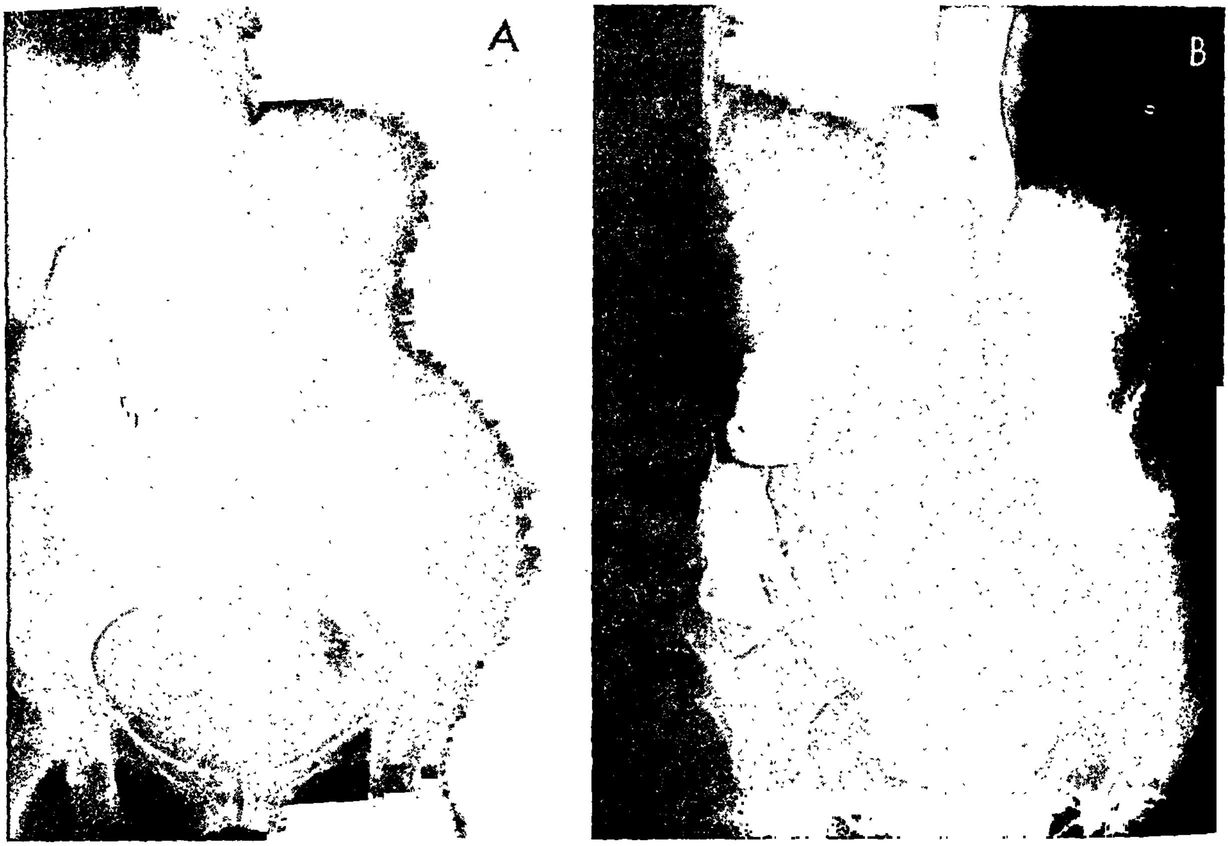

Fig. 1 (case 4).—Acute gastric dilatation of unknown cause. Abdominal film made with patient in recumbent position (shows the enlarged stomach, outlined in part by air in displaced intestines. Vague translucent shadow over lumbosacral area caused by air in stomach. Contrast medium studies (*B*) disclose compression and displacement of colon and obstruction esophagus.

the removal of the cast a physical examination of the abdomen disclosed generalized abdominal distention without tenderness. Radiographic examinations at this time (fig. 3*A*, *B*, and *C*) showed a gastric dilatation with a predominant amount of fluid. Intubation was carried out immediately, and 3,000 cc. of bile stained fluid were withdrawn. Continuous gastric suction was applied for 24 hours and then discontinued. The next day an examination again disclosed gastric distention. Suction was reinstituted. Four days later, a second gastrointestinal examination showed normal findings (fig. 3*D*). Gastric suction was continued for several more days and then the patient was placed on a liquid diet and finally on a solid diet. He was discharged from the hospital without a reapplication of the cast.

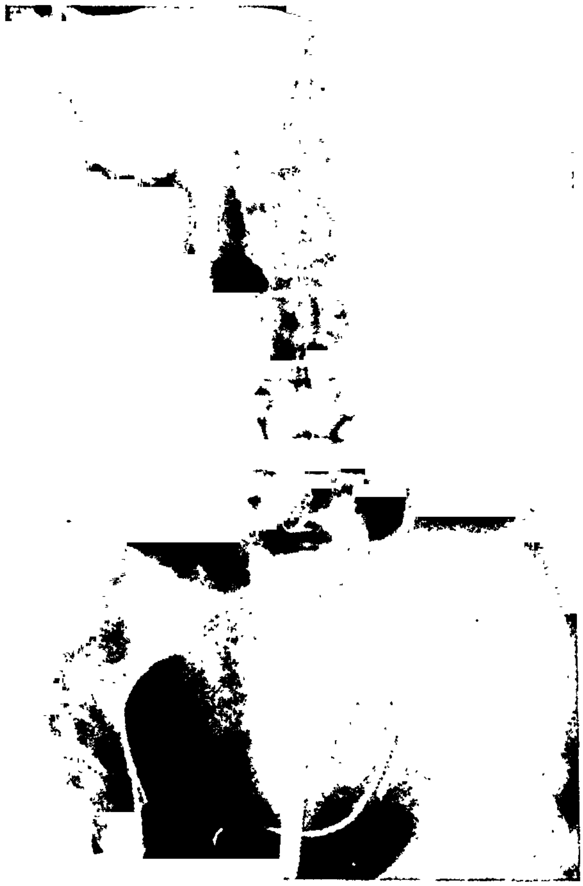

Fig. 2. (case 1).—Acute gastric dilatation after cystoscopy. mach and duodenal cap are markedly distended, princi- lly with air. Rectal tube can be seen. Calculus in left kid- y is well visualized because of superimposed air.

CASE 3.—A 59-year-old man sustained multiple juries to the chest, upper abdomen, and right etabulum in an automobile accident on May 31, 59. The chest injuries were the result of a blow the steering wheel of the automobile. An emergency electrocardiogram showed evidence of myocardial damage. A chest examination disclosed multiple rib fractures and acute pulmonary edema. The upper part of the abdomen was visible on this chest film and showed a mild amount of air in the stomach and a moderate distention of the transverse colon. Bilateral leg casts were applied, but no body cast was placed on the patient. On June 6 the patient complained of abdominal distention and vomiting. An abdominal film at this time (fig. 4*A*) disclosed marked distention of the stomach, predominantly with air, moderate distention of the entire colon, and mild distention of multiple loops of small intestine. An esophageal examination showed a partial obstruction at the cardia, presumably related to the enlarging stomach (fig. 4*B*). After this gastric suction removed 2,000 cc. of fluid, plus large quantities of air. The next day 800 cc. of fluid were removed. The patient experienced no further gastric distention after this.

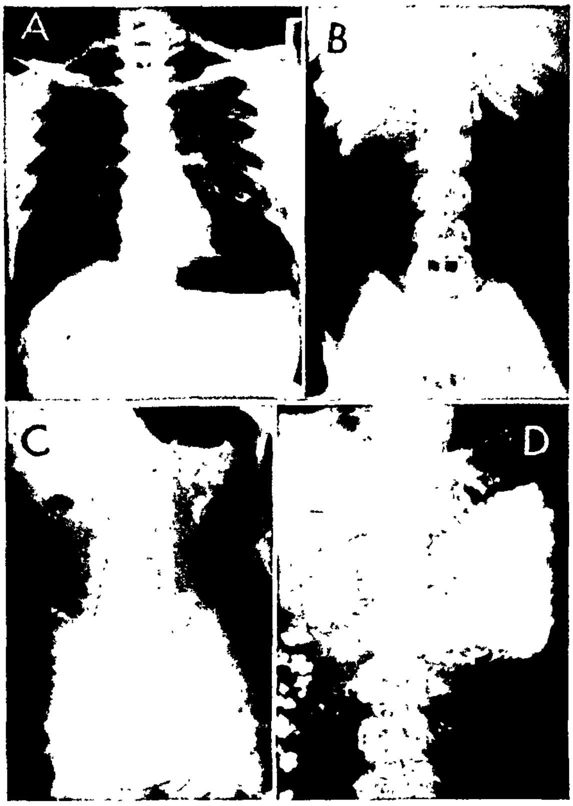

Fig. 3 (case 2).—Acute gastric dilatation after application of body cast for fracture of right femur. Upright chest film (*A*) and recumbent abdomen film (*B*) disclose the gastric dilatation, which predominates in fluid. After oral administration of contrast material (*C*), extent of dilatation can be appreciated. After treatment, second gastrointestinal examination six days later (*D*) discloses normal findings.

CASE 4.—A 69-year-old woman suffered from nausea and vomiting of four days' duration and after that from progressive abdominal distention and cramping pain. For two days she could retain no ingested food or fluid. There was no previous history of abdominal complaints of any type except constipation, for which she frequently took laxatives. Physical examination disclosed an acutely ill patient with marked distention of the abdomen. There was no visible or audible peristalsis in the abdomen and no obvious cause for her illness.

An abdominal radiographic examination, made with the patient in recumbent position, revealed the presence of a large mass filling the middle part of the abdomen (fig. 1*A*). On the same day, a barium enema and an upper gastrointestinal examination were made (fig. 1*B*) and showed the colon to be intrinsically normal but displaced by the abdominal mass. The lower esophagus was obstructed, and on the film several linear streaks of barium could be seen at the distal end of the esophagus, suggesting a volvulus of this structure. No barium entered the stomach. The radiographic impression from these studies was that the patient had gastric distention and esophageal obstruction resulting from the distention. Gastric intubation was unsuccessful. Esophagoscopy was performed, but the esophagoscope could not be passed into the stomach and no fluid could be withdrawn. Since the patient's admission her condition had become steadily worse; the morning after admission her pulse became imperceptible and within a short time she died.

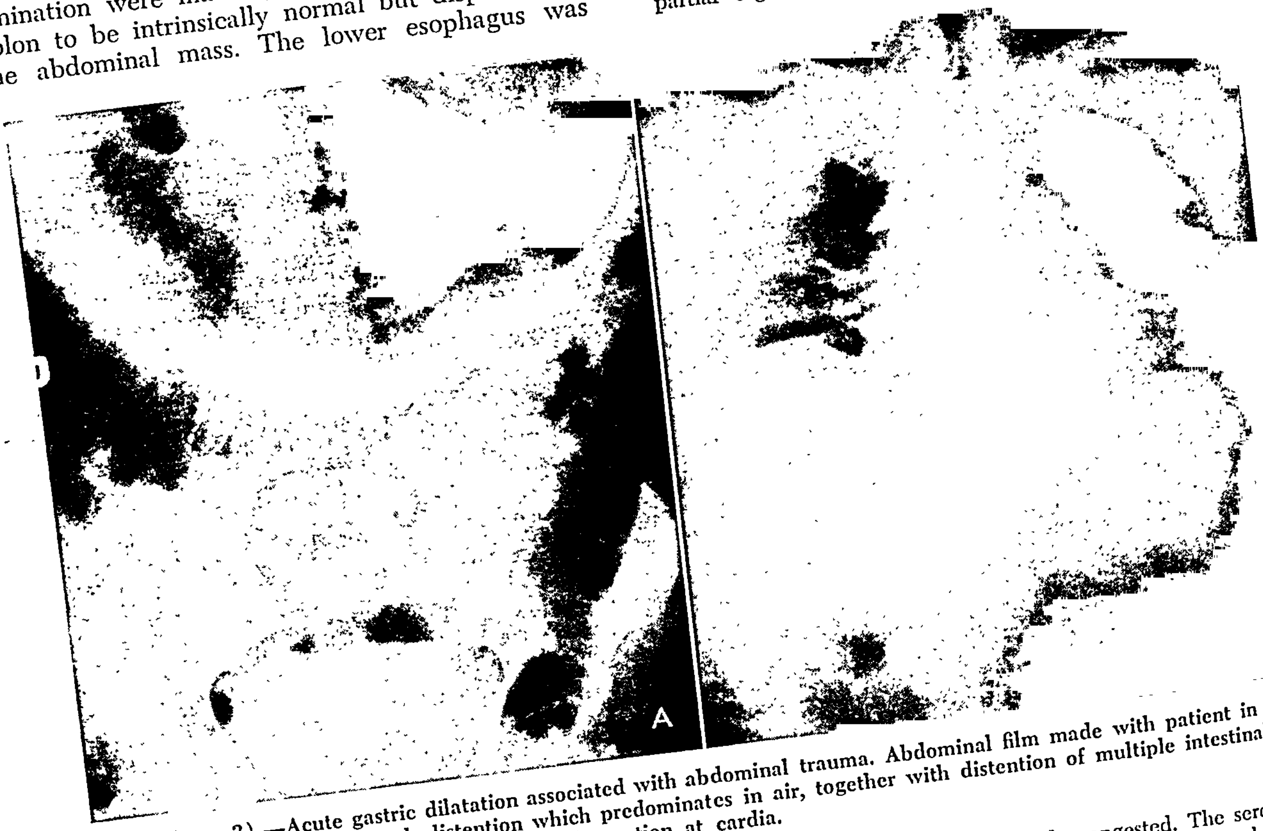

Fig. 4 (case 3).—Acute gastric dilatation associated with abdominal trauma. Abdominal film made with patient in recumbent position (*A*) shows stomach distention which predominates in air, together with distention of multiple intestinal loops. Esophageal examination (*B*) discloses partial obstruction at cardia.

A postmortem examination was performed, and part of the report read as follows:

> The peritoneal cavity contains approximately 3,000 cc. of rather foul smelling, brownish, watery fluid. Upon opening the cavity, a large amount of air also escapes. Upon examining the stomach, this entire organ is markedly discolored, and greenish-black in color. The stomach contains a large perforation measuring 4 to 5 cm. in diameter on its anterior surface near the lesser curvature. This perforation is located 6 cm. below the esophago-gastric juncture. The entire wall of the stomach is markedly thinned and falls apart very rapidly upon manipulation. The marked discoloration and thinning of the gastric wall ends abruptly at the pylorus. The duodenal mucosa appears essentially normal. There is no obstruction present at the pylorus. There is early acute peritonitis present. Microscopic examination of the stomach shows complete autolysis of the mucosa and partial digestion of the remainder of the stomach wall. The blood vessels are intensely congested. The serosal surface of the stomach shows an early polymorphonuclear leukocytic infiltration.

Summary

Acute gastric dilatation is a condition characterized by clinical findings of vomiting, abdominal distention, and collapse. The gravity of this condition in most instances makes mandatory its prompt recognition and treatment. The diagnosis can be quickly and easily established by proper radiographic examination of the abdomen. The necessary examination can be carried out at the bedside as well as in the radiology department.

The radiographic examination further aids in the differentiation of this condition from other abdominal conditions which show similar clinical findings.

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LONG-TERM MANAGEMENT OF OBESITY IN A UNION HEALTH CENTER

ANALYSIS OF SUCCESSES AND FAILURES

Donald Berkowitz, M.D.
and
Nathaniel Beck, M.D., Philadelphia

Seven men and 93 women, each overweight by at least 20% of their calculated ideal weight, started a reduction program. The general plan of management included education, caloric restriction, anorectics, exercise, and psychotherapy. The results were appraised at the end of one year for the participant's success or failure to attain and then to stay at a normal weight. Twenty-six patients discontinued the program although they had lost some weight. Twelve were discharged because they failed to adhere to the program. Most of these people had regained weight during the year. Of the 62 continuing to the end of the year, 42 had lost 20 or more pounds, and 20 had not. Six succeeded in attaining normal weight levels. Three factors which apparently influenced those who failed were lack of motivation, lack of intelligence, and severe emotional difficulties.

Much has been spoken and written in recent years on the subject of obesity. A clearer understanding of the multiple etiological and psychological factors has been obtained [1] as well as more precise data concerning the various pathophysiological and metabolic disturbances frequently associated with the obese state.[2] More anorectic agents are being recommended for appetite suppression, and even hypnosis has its advocates.[3] However, the management of the overweight patient over the long term is rarely mentioned, and careful follow-up studies are lacking in otherwise prolific literature.

We have had the opportunity to observe a large number of obese patients for a prolonged period of time during their course of attempted weight reduction. This report describes our experiences in this endeavor.

Material

One hundred consecutive patients who were referred to the obesity clinic of a union health center were selected for study. There were 93 women and 7 men in the group. The ages ranged from 18 to 72 years, and most were in the 30-to-60-year age category. The initial weights varied from 151 to 320 lb. (68.5 to 145.5 kg.), each patient weighing at least 20% more than his ideal weight as calculated from standard height-age-weight tables.

Method of Treatment

The general plan of management included education, caloric restriction, anorectics, analeptics in some cases, exercise, and psychotherapy. Prior to initiation of therapy, a complete record of the patient's history was made and a physical examination

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From the Sidney Hillman Medical Center of the Male Apparel Industry of Philadelphia, the Einstein Medical Center, and the Hahnemann Medical College.

was performed. A blood cell count, urinalysis, determination of blood sugar and cholesterol levels, and measurement of basal metabolic rate were performed routinely. An electrocardiogram and chest x-ray were taken. In a selected number of cases more elaborate metabolic studies, including a glucose and radioactive fat tolerance test plus liver function evaluations, were done initially and after a significant amount of weight had been lost. These results will be reported separately.

The basic essentials of good nutrition were discussed with each patient, and an attempt was made to distinguish between the many facts and fancies which are so commonly held to by obese persons. The methods for calculating caloric restricted menus were demonstrated by means of the various visual aids furnished by the American Diabetes Association and the American Medical Association. The word "diet" was carefully avoided because it connotes starvation to the average overweight patient.

An anorectic agent, levoamphetamine alginate (Levonor) was administered three times daily either before meals or during the middle of the morning, late afternoon, and at 8:00 p. m. In a certain number of cases levoamphetamine alginate and also methamphetamine alginate were prescribed. Posture control and moderate exercises were demonstrated and encouraged to be followed daily. Each patient was seen at two to four week intervals. The program was continued for one year.

Number of Patients Who Had Lost or Gained Weight One Year After Starting Treatment

	Weight Loss, Lb.						Weight Gain, Lb.	
Period of Treatment	0-9	10-19	20-29	30-39	40-49	50	1-9	10-19
One year	3	17	22	7	3	4	..	..
Less than one year								
Discharged*	..	..	3	3	..	..	..	..
Failed to continue	19	..	..	..	..	..	16	3

* Discharged because of adequate weight reduction.

Results

Fifty-six of the 100 patients were still attending the clinic after one year. Six had been discharged previously because their weight had been restored to normal. An analysis of the individual weight losses in this group of 62 patients revealed extreme variability (see table). Greater reduction usually occurred in those who weighed the most prior to therapy. Forty-two of this group lost more than 20 lb. (9.1 kg.) during the year, 17 lost from 10 to 19 lb. (4.5 to 8.6 kg.), and 3 lost less than 10 lb. (4.5 kg.). The maximum weight loss was 70 lb. (31.8 kg.) in a 45-year-old woman who originally weighed 320 lb.

Twenty-six persons who initially lost some weight failed to return after several visits to the clinic. Twelve others were discharged because they failed to adhere to the program. Follow-up examination of this group of 38 patients revealed that in practically every case an increase in weight occurred after treatment was discontinued. In 19 of the 38 persons the weight was actually greater one year after they had started the program.

Comment

Stunkard[4] has recently reviewed the literature dealing with the results of treatment for obesity. In his critical analysis he has emphasized two important points—the inadequacy and misleading aspects of most published papers and the generally poor results obtained in most of the studies in which adequate data and follow-up statistics are available.

The usual report deals with the management of small groups of persons for short periods of time, usually 4 to 12 weeks, with one of any number of anorectic agents currently available.[5] The results usually indicate that weight reduction was satisfactory in most of the subjects treated. Individual responses, however, are frequently obscured by the reporting of data in terms of averages for the entire group. The fact that most short-term weight reduction studies are favorable regardless of the type of diet or drug used is usually neglected.

Long-term treatment of the obese patient has invariably given poor results, with the finding that most of the patients were unable to lose even 20 lb.[6] In Stunkard's group of 100 obese persons only 12 succeeded in losing this amount.[4]

In our study, 38% of the patients who started on the weight reduction program did not continue. Moreover, an additional 20 who did continue failed to lose 20 lb. even after one year. However, on a more optimistic note, 42 of the original group were successful in losing this amount. This corresponded to 68% of those who persevered through the year's treatment.

Analysis of Successes and Failures

We have tried to analyze our successes and failures to see if there were any common denominators which would enable us to predict in which patients weight reduction would be successful. No objective criteria which could be used to prognosticate were forthcoming, however. Failure or success of the reducing program was not dependent in any way on age, sex, duration of obesity, family history, hypertension, carbohydrate metabolism, or cholesterol levels. This is unfortunate, for if such a scheme were possible it would certainly avoid much "wear and tear," frustration, and disappointment on the part of the physician as well as the patient.

In our experience three factors considered important reasons for failure were lack of motivation, lack of intelligence, and a severe emotional overlay.

Lack of Motivation.—No patient can hope to lose weight successfully if a genuine desire to do so is lacking, because inevitably the program involves self-deprivation and restriction to a point that is often unpleasant, if not uncomfortable. Fifty per cent of our failures belonged in this category.

Lack of Intelligence.—We considered lack of intelligence to be the basis for failure in 20% of our patients. A basic understanding of the aims of dietotherapy is a prerequisite before treatment can be undertaken. Where the lack of intelligence is great, or where language difficulties preclude the patient from comprehending, failure is inevitable. Blind obedience to a specifically prescribed menu for any prolonged period of time has been impractical. Each patient must be re-educated in his eating habits and encouraged to learn as much about the science of nutrition as possible. We have found the use of the exchange system of food values to be of great help in this respect.

Emotional Overlay.—In another 20% of our failures emotional overlay was considered to be of prime importance. The role of the psyche in obesity has been well established. To many people, eating is a compulsive act—a substitute for satisfaction which should be obtained by other means. In this group, headache, nervousness, irritability, dizziness, and depression were noted and were relieved only by the ingestion of food. These side-effects of dieting have also been emphasized by others.[7]

Other Factors.—Other factors which contributed to the ultimate inability of the patient to lose weight included specific intolerances to certain prescribed drugs and concomitant diseases such as severe arthritis which prevented any major degree of ambulation.

Successful Results.—Success, on the other hand, was more difficult to predict. Many patients who on initial impression were considered likely to succeed subsequently failed to continue with their treatment and did not lose weight. The results of previous attempts were of no value prognostically. Several patients who had been able to reduce satisfactorily on other occasions were unsuccessful during this course. Conversely, over 50% of the successful group had failed in each previous try. This was probably a reflection of the interest and vigor with which the present obesity clinic was maintained.

An over-all appraisal, therefore, of our experiences confirms that, as has been found many times before, the treatment of the obese patient is a tremendously difficult task. Success in this respect over the long term may be anticipated in less than half of those who come under our care.

As dismal as the outlook may appear, it should serve as a stimulus and challenge. Certainly, continued treatment is better than no treatment, as is evidenced by the follow-up weights of those who failed to continue with their prescribed regimen. As long as the physician continues to be interested in his patients, sympathetic, kind, and understanding and applies whatever new techniques become available, the future may hold some promise of greater success than is presently obtainable.

Summary

The results of treatment of 100 obese patients in a union health center were analyzed after a one-year period of follow-up. Fifty-six patients were still under treatment after this time. An additional six had been discharged previously because of a satisfactory weight loss. Forty-two of this group lost more than 20 lb. (9.1 kg.) during the year. Thirty-eight per cent failed to continue with the reducing program, although many lost weight initially. The three factors that appeared to be important reasons for failure were lack of motivation, lack of intelligence, and a severe emotional overlay.

101 S. 20th St. (Dr. Berkowitz).

The levoamphetamine alginate used in this study was supplied as Levonor by Nordson Pharmaceutical Laboratories, Irvington, N. J.

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CLINICAL NOTES

CORONARY ARTERIOVENOUS FISTULA INTO MAIN PULMONARY ARTERY

PREOPERATIVE DIAGNOSIS BY SELECTIVE AORTOGRAPHY

Kurt Amplatz, M.D., Jeorge Aguirre, M.D.
and
C. Walton Lillehei, M.D., Minneapolis

Abnormal communications between the coronary arteries and the coronary veins, right atrium, right ventricle, or pulmonary arteries are usually referred to as coronary arteriovenous fistulas. Steinberg and associates,[1] in an excellent review of this subject, found 22 reported cases and added one case diagnosed by forward angiography.[1A] It is the purpose of this article to present an unusual case which was accurately diagnosed by selective aortography and successfully treated by surgical excision.

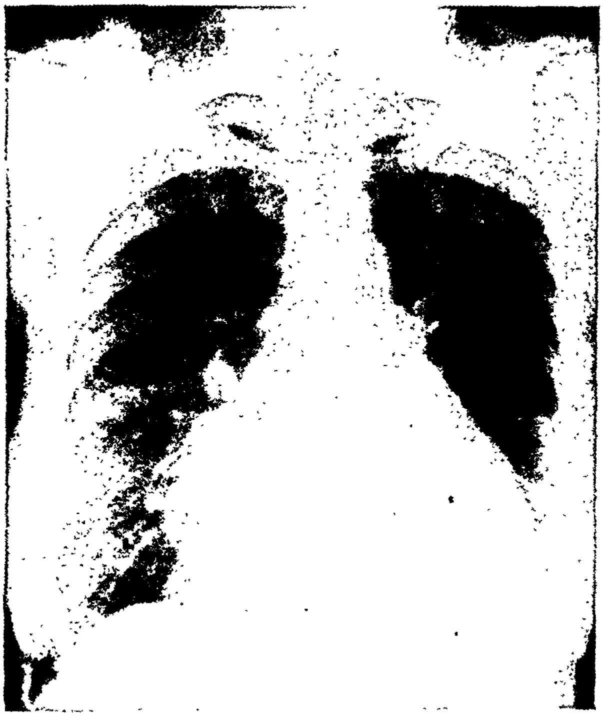

Fig. 1.—Marked, generalized, unspecific cardiac enlargement, without roentgenographic evidence of left-to-right shunt.

Report of a Case

A 53-year-old woman was admitted to the University Heart Hospital on Feb. 22, 1959, complaining of shortness of breath. She had always been in good health until October, 1958, when she noticed the onset of exertional dyspnea and increasing fatigue. In December, 1958, she was hospitalized for acute heart failure and given treatment with digitalis, diuretics, and sedatives. In 1953, when she had a hysterectomy, results of an examination of her heart had been recorded as normal. On admission, physical examination revealed the heart to be generally enlarged. No thrill was palpable. A loud continuous murmur was heard over the pulmonic area, with maximal intensity over the second and third left intercostal spaces. The murmur was not transmitted to the back. Blood pressure was 160/100 mm. Hg in the upper and lower extremities. The electrocardiogram showed left ventricular hypertrophy with left ventricular strain. The possibilities of aortic valvular disease, patent ductus arteriosus, or ruptured sinus of Valsalva were considered.

Cardiac fluoroscopy and heart films indicated a generally enlarged heart, without roentgenographic evidence of a left-to-right shunt, (fig. 1). A retrograde aortogram, with the catheter in the ascending aorta, was performed[2] and showed the presence of an arteriovenous malformation obviously being fed by the left coronary artery (fig. 2 and 3). Opacification of the pulmonary artery without staining of the right ventricle indicated a direct shunt from the coronary artery fistula into the pulmonary artery. During right heart catheterization radioactive methyl iodide curves were obtained from the pulmonary artery and right atrium.[3] A typical but delayed left-to-right shunt curve was obtained from the pulmonary artery which was consistent with a 1.7 vol. per cent oxygen increase at this level. Early appearance of radioactivity in the blood samples from the right atrium suggested an additional smaller arteriovenous communication from the coronary artery fistula to the coronary sinus or directly to the right atrium (fig. 4).

On March 6, 1959, a thoracotomy was performed on the left side. Just as the pleura was entered, the anesthesiologist reported that he was unable to obtain a blood pressure reading; therefore, the pericardium was rapidly opened. The heart was

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Instructor of Radiology (Dr. Amplatz); Medical Fellow of Surgery, (Dr. Aguirre); and Professor of Surgery, (Dr. Lillehei); University of Minnesota Hospitals.

seen to be still feebly beating and the visible myocardium was of a deep cyanotic color. Immediately a small serrefine clamp was applied, occluding the main parent artery feeding the fistula, and the heart responded at once with contractions of increasing vigor. The blood pressure returned to the preanesthetic level and remained stable for the rest of the operation. A large cavernous mass of vessels was present between the left atrial appendage, base of the pulmonary artery, and origin of the left anterior descending coronary artery. This conglomerate of twisted vessels was fed by the left main coronary artery, which measured 1 cm. in diameter. The anterior descending and circumflex branches were of normal size. The arteriovenous malformation communicated with the main pulmonary artery just distal to the pulmonic valve through three openings. The parent artery (8 mm. in diameter) was divided at its origin from the very large left main coronary artery, and the fistulous mass was excised. Proceeding toward the communication into the main pulmonary artery, five or six smaller feeding arteries and veins were encountered descending directly into the underlying myocardium. These direct communications with the coronary veins probably accounted for the suggested left-to-right shunt at the atrial level on the radioactive methyl iodide curves. After the excision of the fistula, the initially present thrill disappeared; the patient made a rapid recovery and was discharged 14 days after operation. A recent follow-up examination disclosed the absence of cardiac murmurs and a continued dramatic improvement in the patient's exercise tolerance.

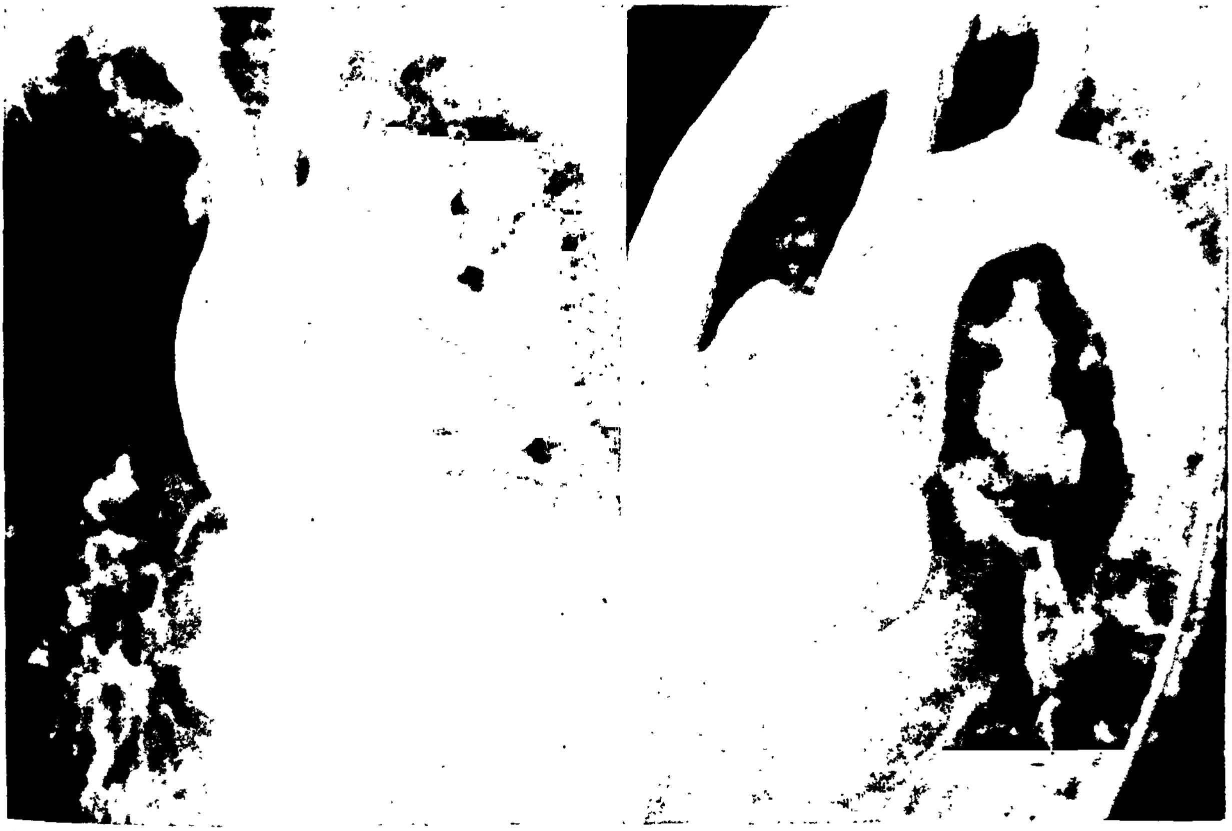

Fig. 2.—*Left,* selective aortography demonstrating coronary artery fistula feeding main pulmonary artery. *Right,* lateral view showing aortic cusps being opened during systole, with coronary artery fistula and opacified pulmonary artery well visualized.

Comment

During the past 12 months at the University of Minnesota Heart Hospital four patients ranging in age from 17 months to 53 years have been correctly diagnosed preoperatively as having a coronary arteriovenous fistula (two into the right ventricle, one into the right atrium, and one [the present patient] into the pulmonary artery). Three operations have been performed to the time of writing, all resulting in successful excision of the shunt with murmurs absent postoperatively. In three of these patients selective aortography was performed by means of a catheter placed into the ascending aorta, and in each the precise site of the fistula was clearly demonstrated. Selective aortography is considered to be the best method of diagnosis in patients with this type of heart lesion.

The immediate favorable response to clamping off the main feeding branch of the arteriovenous malformation showed the unique physiological burden of coronary arteriovenous fistulas on the myocardium. The specific hemodynamic effect of an arteriovenous communication is the loss of capillary resistance in the particular vascular bed. This decrease results in compensatory factors such as increased cardiac output, increased blood volume, and generalized vasoconstriction.

The normal heart may compensate well in large left-to-right shunts for long periods of time by virtue of an increased output. In arteriovenous fistulas involving the coronary circulation, the ability of the heart to compensate for these abnormal shunts is greatly reduced by direct effect on the myocardial blood supply. The fact that interarterial communications between the right and left coronary artery beds in man are limited further aggravates the effects of the fistula.[4]

Since these patients also are more susceptible to bloodstream infections and cardiac decompensation, diagnosis is sufficient indication for surgical intervention. Excision is the preferred method of treatment, since mere ligation is likely to lead to recurrence.

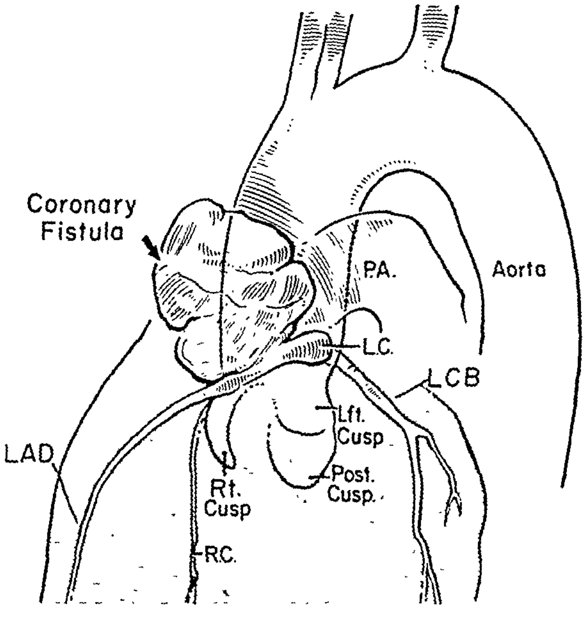

Fig. 3.—*L.C.:* left main coronary artery. *R.C.:* right coronary artery. *LCB.:* left circumflex coronary artery. *P.A.:* pulmonary artery (branch).

Summary

Coronary artery fistulas are 10 times less common than left heart tumors[1] but are now being more frequently identified.[5] Coronary artery fistulas cause progressive cardiac complications and should be surgically excised when diagnosed. Selective aortography has proved to be the preferred method for diagnostic purposes.

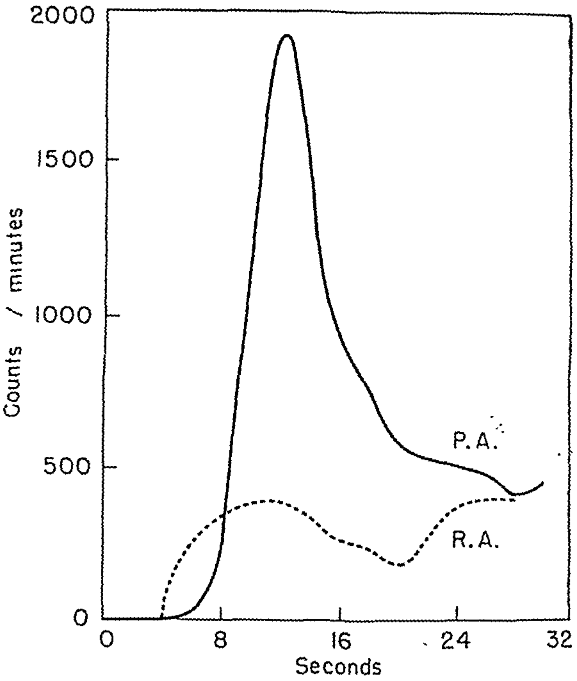

Fig. 4.—Radioactive methyl iodide curves obtained by sampling from pulmonary artery and right atrium. Note typical but delayed left-to-right shunt curve at pulmonary artery level, probable smaller left-to-right shunt at right atrial level.

A 53-year-old woman with a fistula between the left-main coronary artery and the pulmonary artery underwent operation and made a complete recovery after diagnosis had been established by selective aortography.

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PALATABLE VEGETABLE-OIL MILK

Theodore W. Houk, M.D., Seattle

Because of the widespread use of diets low in saturated fats, many patients are restricted to the use of skim milk as a substitute for whole milk. Many of these same patients are instructed to take vegetable oil as a substitute for animal fat. The following recipe for a vegetable-oil milk was devised to meet the foregoing requirements and to provide the satiety value of a palatable whole milk.

Materials and Method

Five and one-half cups of cold water, 2 cups of powdered skim milk, 2⅓ oz. of vegetable oil, e. g., corn oil, cottonseed oil, or peanut oil, and between 4 and 13 drops of butter flavor, depending on individual preference, will make 1½ qt. of "milk." Place the cold water in a 2-qt., narrow-mouthed fruit jar. Stir in the powdered skim milk. Add the oil and butter flavor. Attach the beater head of a high-speed electric blender to the 2-qt. jar. Blend at high speed for seven minutes. The mixture should be stored in the refrigerator.

After several hours most of the foam will have settled. In pouring the milk the remaining foam may be held back with a tablespoon. Sometimes a little cream-like material will rise to the top of the jar, but this can be readily dispersed by shaking.

When varying the total quantity of the recipe, the blending time as well as the individual ingredients must be varied in direct proportion to the total quantity of the recipe. Individual ingredients may be varied slightly to suit the taste. The preparation contains about 23 calories per ounce.

A palatable 20% cream-like material for use in coffee can be prepared by blending 1 cup of cold water, ⅓ cup of skim milk powder, 2 oz. of vegetable oil, and 4 to 12 drops of butter flavor for two minutes in a pint jar.

337 Stimson Bldg. (1).

Director of Medical Education, Providence Hospital.

PRELIMINARY COMMUNICATION

COMPARATIVE CLINICAL EVALUATION OF TWO ALKYLATING AGENTS

MANNITOL MUSTARD AND CYCLOPHOSPHAMIDE (CYTOXAN)

Rose Papac, M.D., Nicholas L. Petrakis, M.D., Fari Amini, M.D.
and
David A. Wood, M.D., San Francisco

An intensive search for agents of increased therapeutic benefit in the treatment of neoplastic disease has prompted the development of newer alkylating agents. To meet the requirement of increased clinical efficacy, it is necessary that such compounds exert more selective action and fewer side-effects and have dimished toxic properties.

On the basis of animal testing, numerous alkylating compounds demonstrate tumor-inhibiting properties which exceed that of mechlorethamin hydrochloride (nitrogen mustard). Clinical trials with two such agents form the basis of this report.

Mannitol mustard (Degranol), also called mannomustine (British Pharmacopeia) and with a chemical structure of 1-6-(dibetachloroethylamino)-1, 6-deoxy-D-mannitol dihydrochloride (fig. 1) was synthesized by Vargha and co-workers.[1] This modification of the alkylating group was introduced with the supposition that cell membranes could be readily permeated by substances, namely the sugars, which take part in cell metabolism.

Cyclophosphamide or N-N-di (beta-chlorethyl)N' O-propylenephosphoric acid ester diamide (Cytoxan, Endoxan, [fig. 1]), synthesized by Arnold and co-workers,[2] was also developed in an attempt to increase the selectivity of cytotoxic action. It was postulated that the phosphamide group might well be attacked by enzymes (e.g., phosphatases, phosphamidases) which are present in large amounts in tumor tissue, and that this group would then liberate the active betachloroethyl group at the desired site of action.

Materials and Methods

Thirty-two patients with advanced carcinomas and lymphomas have been treated with mannitol mustard since August, 1958. Thirty-one patients

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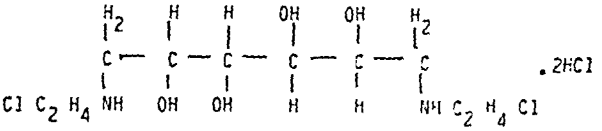
From the Cancer Research Institute and the Department of Medicine, University of California Medical Center.

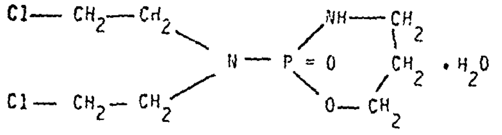
with these diseases have been treated with cyclophosphamide since January, 1959. In each group lymphomas constituted about one-half of the cases.

The clinical and hematological evaluations were carried out at weekly intervals for 6 to 10 weeks and, in most instances, monthly thereafter.



$$\underset{ClC_2H_4NH}{\overset{H_2}{C}}-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-\underset{H}{\overset{OH}{C}}-\underset{NHC_2H_4Cl}{\overset{H_2}{C}}\cdot 2HCl$$

Mannitol Mustard



Cyclophosphamide

Fig. 1.—Chemical structure of mannitol mustard (Degranol) and cyclophosphamide (Cytoxan, Endoxan).

Mannitol Mustard

Administration and Dosage.—Mannitol mustard is supplied as a white powder readily soluble in isotonic sodium chloride solution. It is administered intravenously. In some instances it was given as a single injection but more frequently in divided doses of 5 mg. per kilogram of body weight. The injections did not damage the veins. Extravasation occurred in three instances; only once did superficial ulceration develop, but it healed completely in eight weeks. Intrapleural and intraperitoneal administration of mannitol mustard were each carried out on one occasion. While the drug was well tolerated when administered in this manner, no benefit resulted in either instance.

The dose-response relationship with mannitol mustard, expressed as that dose which produced a leukopenia of 2,000-3,000 cells per cubic millimeter, is shown in figure 2. Each point on the graph represents the cumulative percentage of the total number of persons who, having received a given dose, showed such a response. These data are derived from the solid tumor and lymphoma groups combined. The median effective dose which induced such a response in 50% of the patients is 12.8 mg. per kilogram of body weight.

Side-Effects.—The most prominent side-effects of therapy with mannitol mustard were nausea and vomiting, which developed in all but six patients. In most instances this was related to the dose given; with administration of a divided dosage and the use of phenothiazine drugs, however, these effects were controlled. Total doses of 10 mg. per kilogram of body weight or less were seldom associated with gastrointestinal side-effects.

Cyclophospamide (Cytoxan)

Administration and Dosage.—Cyclophosphamide is available as a water-soluble white powder, 5 cc. of distilled water being added to 100 mg. of the powder. It is also supplied in 50-mg. tablets for oral use. Intravenous administration did not result in damage to veins. Intrapleural and intraperitoneal use were similarly well tolerated.

In three instances the drug was given as a single dose; usually it was administered in divided doses for a total dose range of from 20 to 40 mg. per kilogram of body weight, intravenously. The orally given dose ranged from 56 to 126 mg. per kilogram of body weight.

The dose-response relationship of cyclophosphamide which induced a leukopenia of 2,000-3,000 cells per cubic millimeter is shown in figure 3. With the orally administered preparation, each dose level was represented by a single patient, but with the intravenously given preparation each dose level was studied in from 1 to 12 persons. The straight-line character of this response indicates in this figure, as in the preceding one, that a normal distribution is present. The median effective dose of cyclophosphamide is 70 mg. per kilogram of body weight for the orally given preparation and 25 mg. per kilogram of body weight if given intravenously.

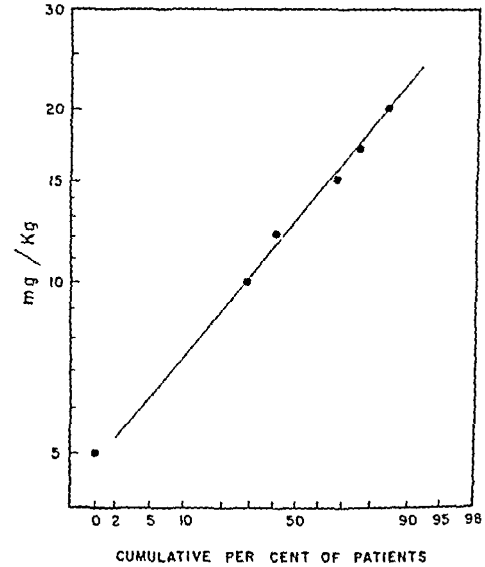


Fig. 2.—Effective doses resulting in peripheral white blood cell count of 2,000-3,000 per cubic millimeter with mannitol mustard therapy.

Side-Effects.—Nausea and vomiting developed in 13 patients treated with cyclophosphamide. These symptoms occurred in relation to the dosage of the drug which had been given and seldom developed if the daily dose was 200 mg. or less. Oral administration of the drug was not associated with gastrointestinal symptoms.

Alopecia, noted in 10 patients treated with cyclophosphamide, was the most troublesome side-effect. It was extremely severe in five patients, four women and one man. In these five instances the alopecia was diffuse; in the other patients it was patchy in distribution. Loss of axillary or pubic hair was not noted. Regrowth of hair occurred in 10 to 12 weeks.

Results

The results of therapy are summarized in tables 1 and 2. The criteria applied are those defined by Galton and co-workers.[3] Benefit refers to absence of signs or symptoms of disease for at least six months; effect refers to improvement of lesser extent or duration; no effect implies that the drug was therapeutically ineffective in terms of objective manifestations of disease.

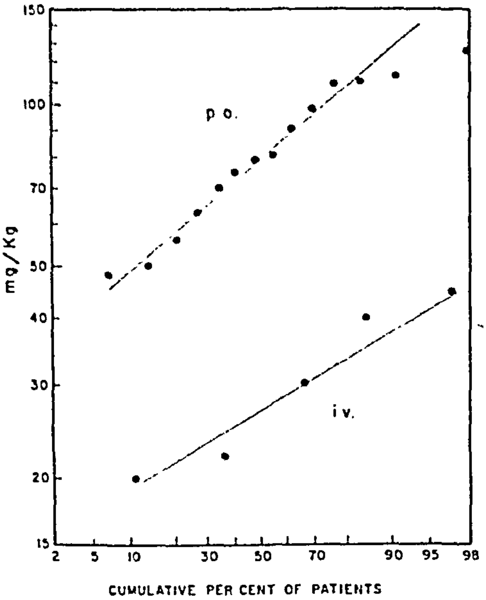


Fig. 3.—Effective doses resulting in peripheral white blood cell count of 2,000-3,000 per cubic millimeter with cyclophosphamide therapy.

Mannitol Mustard Therapy.—Three patients with lymphosarcoma derived substantial benefit from mannitol mustard therapy, one being free from clinical evidence of disease for 12 months. Below, a summary of this case is presented:

Report of a Case: A 73-year-old retired baker developed painless cervical lymphadenopathy on the left side in October, 1956. A biopsy specimen taken in February, 1957, revealed the presence of lymphosarcoma. Radiotherapy to the cervical region resulted in disappearance of the enlarged lymph node. In August, 1958, recurrent cervical masses and generalized lymphadenopathy with hepatosplenomegaly were noted. Peripheral blood cell count and bone marrow findings were within normal limits. An x-ray of the chest revealed mediastinal and hilar masses. On Nov. 18, 1958, the patient received 10 mg. per kilogram of body weight of mannitol mustard intravenously. Within a week marked regression of peripheral lymphadenopathy was evident, and within eight weeks there was complete regression of the enlarged lymph nodes as well as reduction in hepatosplenomegaly. One year later the patient showed no evidence of recurrence.

TABLE 1.—*Results of Treatment with Mannitol Mustard in Thirty-two Patients*

Diagnosis	No. of Patients	Results		
		Benefit	Some Effects	No Effect
Lymphosarcoma	6	3	3	
Reticulum cell sarcoma	4		3	1
Hodgkin's disease	3		3	
Chronic granulocytic leukemia	1		1	
Carcinoma of ovary	3		1	2
Carcinoma of intestine	3			3
Carcinoma of lung	2			2
Carcinoma of prostate	1			1
Carcinoma of breast	1			1
Carcinoma of bladder	1			1
Carcinoma of biliary tract	1			1
Wilms's tumor	1			1
Melanoma	1			1
Thymoma	1			1
Anaplastic carcinoma	3			3
Totals	32	3	11	18

In the solid tumor group, the most notable response was achieved in a patient with ovarian carcinoma who had recurrent ascites and palpable abdominal masses, both of which regressed after mannitol mustard therapy.

TABLE 2.—*Results of Treatment with Cyclophosphoramide (Cytoxan) in Thirty-one Patients*

Diagnosis	No. of Patients	Results		
		Benefit	Some Effects	No Effect
Lymphosarcoma	7	3	4	
Hodgkin's disease	3		3	
Reticulum cell sarcoma	3		3	
Acute leukemia	1		1	
Carcinoma of ovary	3		3	
Carcinoma of lung	3			3
Adrenal carcinoma	1			1
Wilms's tumor	1			1
Melanoma	1			1
Pseudomyxoma peritonei	1			1
Carcinoma of colon	1			1
Carcinoma of prostate	1			1
Carcinoma of stomach	1			1
Embryonal carcinoma of testis	1		1	
Anaplastic carcinoma	2			2
Hypernephroma	1			1
Totals	31	3	15	13

Cyclophosphamide Therapy.—Three patients with lymphoma obtained significant benefit from cyclophosphamide treatment. Below, a brief summary of one of these cases is presented:

Report of a Case: A 57-year-old machine-shop worker noted cervical enlargement on the left in May, 1958. In December, 1958, generalized lymphadenopathy was present and an inguinal node biopsy specimen revealed the presence of lymphosarcoma. An x-ray of the chest demonstrated hilar masses on the left. From April 29, 1959, to May 6, 1959, cyclophosphamide, 40 mg. per kilogram of body weight, was given. Regression of lymphadenopathy occurred four weeks after the last treatment and has persisted to the present time, a period of seven months.

In two patients with ovarian carcinoma suppression of ascites and regression of the palpable tumor masses occurred as a consequence of cyclophosphamide therapy.

In the patient with acute leukemia, the peripheral white blood cell count was reduced from 70,000 to 15,000 per cubic millimeter, with clinical improvement for a period of three weeks. This result, however, is not unique among alkylating agents, for Israels[4] described chlorambucil-induced remission in acute leukemia and Bierman advocated the use of busulfan (Myleran) in this disease. Recently, Bartlow[5] reported that mannitol mustard therapy occasionally achieved a similar response.

Hematopoietic Effects.—Maximum hematopoietic depression occurred from 30 to 45 days after completion of mannitol mustard therapy, with a return to pretreatment values 45 to 60 days later. Lymphocyte depression developed during the period of drug administration and persisted for 7 to 10 days. Granulocyte depression paralleled the peripheral white blood cell count change, occurring 30 to 45 days after therapy. The period of maximum platelet depression was also coincident with the time of leukopenia and frequently was relatively severe. The drug was not given to any patients with known thrombocytopenia prior to treatment. No leukopenia occurred in two cases of lymphoma in which therapeutic benefit occurred.

Intravenous administration of cyclophosphamide generally resulted in a depression of the peripheral blood elements in from 3 to 14 days after completion of treatment, with a return to prior levels in 7 to 10 days. Lymphopenia developed during therapy and persisted until the return of the peripheral white blood cell count to former levels. With oral administration of the drug, the development of lymphopenia was gradual and irregular. When the dose of cyclophosphamide was less than 50 mg. daily, a rise in lymphocytes occurred. Granulocytopenia was seldom remarkable, although in one instance the total granulocyte count fell to 10% of its original level. Since the total dose in this patient was 60 mg. per kilogram of body weight, given orally, the correlation between the development of granulocytopenia and the quantity of drug administered was not marked. Platelet depression was not significant in most instances. In one patient who received a total dose of 109 mg. per kilogram of body weight orally over an 80-day interval, the platelet count was reduced from 200,000 to 85,000 per cubic millimeter. In another patient whose total orally given dose was 113 mg. per kilogram of body weight over an 86-day interval, the platelet count dropped from 400,000 to 120,000 per cubic millimeter. Even with doses producing severe leukopenia, thrombocytopenia was not generally noted.

Comment

From our data it is not possible to state the therapeutic superiority of either mannitol mustard or cyclophosphamide. The cytotoxic effect of each is most notable in that group of human tumors which is generally responsive to the alkylating drugs. There are definite hematological differences in the effects of these compounds which are of interest. These are the differing time interval of marrow depression and the relative degree of thrombocytopenia.

The fact that the time interval of marrow depression varies suggests that the drugs exert their effect on cellular division at different phases of the mitotic cycle, or that they induce a varying degree of prolongation of the mitotic process at the same phase of interruption. Assuming that cellular division is affected at different phases of mitosis by each of these agents, it may be that mannitol mustard reduces the frequency of cell division because of its prolonged depressant effect on hematopoietic elements. This could be accomplished by lengthening of the intermitotic interval, as suggested by Elson[6] in his analysis of the effect of busulfan on the hematopoietic tissue of rats. It could then be postulated that the effect of cyclophosphamide is a destructive interference with cellular division at some other vulnerable phase, presumably early in mitosis or in the immediate premitotic interval.

It is also conceivable that the differences in hematological depression represent variations in quantitative effect. Rosin and Goldhaber[7] have demonstrated that ethyl carbamate (Urethane) induces prolongation of the mitotic process of both normal and leukemic myelocytes in rodents. Perhaps this phenomenon occurs with alkylating agents in general, being more prominent with such agents as mannitol mustard.

Since the spectrum of tumors responding to the use of these drugs is extremely similar, it is probable that the variation in cellular suppression does not represent increased specificity but possibly differing vulnerability, which depends on the proliferative activity of affected cell types.

Since increased specificity cannot be attributed to these agents, their clinical usefulness depends on whether the incidence of fewer toxic properties and side-effects was due to their use. With mannitol mustard therapy there is no evidence of such an advantage. With the use of cyclophosphamide, there is a relative lack of thrombocytopenia and a diminution in gastrointestinal side-effects, so that it may offer therapeutic advantages over other alkylating agents.

The development of newer alkylating agents has provided additional fundamental information to the biochemist and biologist and continues to stimulate investigations directed toward improvement of therapy of human neoplastic disease.

Summary

Mannitol mustard (mannomustine, Degranol) was administered to 32 patients with malignant disease and cyclophosphamide (Cytoxan, Endoxan) to 31 patients with various neoplasms. The best results with each drug were achieved in patients with lymphosarcoma, in whom striking remission occurred in three instances after administration of mannitol mustard and on three occasions with cyclophosphamide therapy.

With intravenous administration, both agents induced nausea and vomiting which was directly related to the dose given. With oral cyclophosphamide therapy this did not occur. Alopecia developed in one-third of the patients treated with cyclophosphamide.

Mannitol mustard appears to offer no particular therapeutic advantage over other alkylating agents. With cyclophosphamide therapy, the relative lack of thrombocytopenia and the absence of gastrointestinal symptoms with oral therapy suggest that it is a useful agent. A comparative evaluation of this agent with such drugs as triethylene melamine or chlorambucil is necessary to determine whether it is superior.

Drs. Calvin Zippin, Jean C. Sabine, and William M. Silliphant aided in the preparation of this paper, and Dr. William A. Atchley assisted in the medical care of the patients. Carla Schultz, Mary Davis, Marie Doherty, Rose Lee, and Lillian Kwok provided valuable technical assistance.

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The mannitol mustard used in this study was supplied by courtesy of Dr. T. Phillip Waalkes, Cancer Chemotherapy Division of the National Cancer Institute, National Institutes of Health; the cyclophosphamide used in this study was supplied as Cytoxan by courtesy of Dr. James M. Tuholski, Mead Johnson & Company, Evansville 21, Ind.

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STEROID THERAPY IN ASTHMA.—The value of corticotropin and corticoids in the short-term treatment of asthma is accepted. Their use does not replace standard treatment with broncho-dilators nor should it prevent a careful search for underlying etiological factors. Long-term treatment is sometimes of value, especially for older patients: it should only be employed in those whose asthma cannot be controlled by other means. . . . There are certain circumstances in which the use of steroids is contra-indicated: these include pulmonary tuberculosis and peptic ulcer, which should be excluded before treatment is commenced. Steps can be taken to minimize the risks in these conditions if the use of steroids is considered necessary to save life as in severe status [asthmaticus]; in pulmonary tuberculosis by simultaneous treatment with appropriate antibiotics; in peptic ulcer with alkalis. If there is evidence of cor pulmonale, the use of corticotropin or salt-retaining corticoids may precipitate failure, but the newer steroid preparations with diminished salt-retaining properties may be given cautiously. Hypertension may be increased. In diabetes mellitus it may be necessary to adjust the dosage of insulin. Long-term treatment of asthma with corticoids is rarely justified if these conditions are present.—R. S. B. Pearson, D.M., F. R. C. P., Steroid Therapy in Asthma, *The Postgraduate Medical Journal,* August, 1959.

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The class of substances grouped together under the generic term RNA as yet has not been resolved into constituents recognizable as individual molecular species. In spite of this difficulty, and of the fact that the structure and function of RNA still are not clearly established, a substantial body of information has been collected concerning biosynthetic pathways of RNA.

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By the time this was established, the important discovery of the enzyme polynucleotide phosphorylase had been made by Grunberg-Manago and Ochoa.[4] This enzyme, found in a variety of microorganisms and now highly purified, catalyzes the formation of RNA-like polynucleotides from the nucleoside dipurine or pyrimidine base, as shown, with R the ribose moiety of the nucleotide and P a phosphoryl group. The attachment to the ribose is on the number 5 carbon atom of the sugar:

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In this reaction one phosphate group is split from each nucleoside diphosphate as the phosphodiester bond of the polynucleotide is formed. The enzyme requires both Mg^{++} and a small amount of a polyribonucleotide or oligoribonucleotide present as a "primer." When a mixture of nucleoside diphosphates (e. g., adenosine, guanosine, cytidine, and uridine diphosphates) is used as substrate, the product is a mixed co-polymer which resembles RNA. If the enzyme acts on a single nucleoside diphosphate, however, the product is a homopolymer consisting of only one type of sub unit. These homopolymers have served as important model substances even though they do not exist naturally.

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VIA PADUA

Venice, Milan, Verona, and Padua, the ancient cities of northern Italy, are famous not only for their beauty but also for their great achievements in the past. Currently they are delightful centers for tourism and historical studies. Padua claims the lion's share of medieval and Renaissance heritage, particularly in the evolution of medicine and anatomy. The University of Padua was outstanding in the emancipation of science from medieval fetters and was noteworthy for its zealous protection of freedom of thought. Venice, the most brilliant commercial city in the world during the 15th century, has lost none of its fascination for the 1960 tourist, even though it appears to be as busy as Times Square on New Year's Eve, with as high a percentage of American faces. Milan is the 20th-century commercial center that is the proud possessor of Leonardo da Vinci's "Last Supper,' 'painted in the master's own medium, on the north wall of the refectory of Santa Maria delle Grazie. Verona, the southern gateway from the Brenner Pass, was the residence in the sixth century of the Ostrogoth king Theodoric, the sovereign who urged that the monks of his realm read Hippocrates and Galen.

But it is Padua, some of her streets and a select few of her illustrious citizens of science, that claims particular attention. As one enters the modern city, an occasional student will be wearing a grey felt hat with a long, pointed peak and a jauntily placed tall feather. This is the mark of a medical student. A collector of headgear will have no difficulty in procuring a sample in one of the town shops. The University of Padua was founded in 1228 A. D. by a band of disgruntled students from the school in Bologna. It owed its spectacular rise in large measure to the learned physician, Pietro d'Abano (1250-1315). As a professor of medicine and author of a highly controversial book he struggled to reconcile the views of the medieval scholastics with the original writings of the Greeks and to dispel the contradictions which were hampering the progress of medicine.

No Via d'Abano commemorates him, but Pietro d'Abano's memory is perpetuated by his statue in one of the city squares. A number of other famous scientists of Padua, however, were honored by streets which were named after them. Thus the Via Fabrizio d'Aquapendente is in the outskirts of the town. Fabricius (1537-1619), the distinguished surgeon and anatomist, attracted students from all over Europe and himself arranged for the building of the famous Anatomical Amphitheater that can be visited today in the municipal museum maintained in a portion of the old university. Only a few blocks removed is the Via Vesalius, which honors the great anatomist Andreas Vesalius (1514-1564) whose *De humani corporis fabrica* revolutionized the study of anatomy. Another street in Padua is the Via Malpighi. Marcello Malpighi (1628-1694), one of the earliest microscopists, added the evidence for the one remaining question in Harvey's concept of the circulation of blood, namely, the discovery of the capillaries. This contribution was made but four years after Harvey's death. Prior to this observation, Harvey assumed the existence of such anastomoses, but was unable to demonstrate them because he worked with the naked eye.

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Near the center of the town a plaque on a small house calls attention to the fact that Dante Alighieri, a presumed acquaintance of Pietro d'Abano, "once lived here." The Via Dante is two short blocks removed from the poet's house.

A portrait gallery in one wing of the municipal museum contains the portraits of many medieval and renaissance luminaries, including all those scientists described in this editorial. If Harvey was overlooked by the Commission for the Naming of City Streets, the oversight is partially balanced by a full-length portrait in the gallery.

As one leaves the Anatomical Amphitheater and the small art gallery through the courtyard, two symbols are prominently visible high on the opposite wall. One is the seal of the city of Padua. To the right of the seal, ineffectively covered at the present time with neutral paint, is a reminder of the Fascist regime. "Il Duce" is plainly legible in the bright sun.

If one or more physicians or anatomists of Padua has been overlooked, a notation to this effect would be welcome. Such an omission might serve as a happy excuse to return to northern Italy and to wander once more along the Via Vesalius or Via del Falloppio. Should this opportunity present prompt action, the traveler might wish to take along at least two books to replace an out-of-date Baedeker. Fielding's Guide to Europe[1] contains helpful general information, while Castiglioni's "History of Medicine"[2] is a volume filled with medical lore.

LEARNING MEDICINE

[Jean Fernel] judged the surest and quickest way of learning medicine was this. After a thorough grounding in the principles and elements of philosophy, to learn straightway from some terse and well-written medical precis such details as have to be known of the nature of the human body; then to master the flavours, powers and virtues of medicaments simple and compound; and then to learn to distinguish the signs and symptoms of the several diseases and their causes, and to gather these together, as a store within the memory; then, finally, to follow, long and attentively, the art of practice of some elderly practitioner, capable and experienced in treatment, and to observe in the sick patients themselves what you have read in the books and heard in the lecture-room. He held that there was much in the theoretical part of medicine which could not be explained truly, nor understood, except by way of long practice and experience. He judged that no one can get through on books alone, numerous although books are. The best instructors in medicine were in his view practice and experience; they clear up the obscure and equivocal which so embarrass and obstruct the beginner, and they fortify him. So it was that he dissented from growing grey in following theory, as in fact most do. Rather should one go forward early into the art of practice, since it is of all teachers the best, but in so doing take for guide an old physician of experience.—C. Sherrington, The Endeavour of Jean Fernel, New York, Cambridge University Press, 1946, page 157.

JEAN FERNEL (1485-1557)

Rising at about 4 o'clock every morning he went from his bedroom down to his library. There he looked over some page of text of the ancient masters, either because he did not feel satisfied about it, or that he did not sufficiently remember it, or in order to add to it something by way of commentary. After that, with the coming of daylight, he went out to his public lectures, or to visit his patients. Then it was that urines were brought to him and he would inspect them. What he opined about them he made known, and ordered treatment according to the cause of the disease, and the constitution of the patient, as far as he could gather those by conjecture.

Back again for his meal, he retired to his library while dinner was being prepared, and when dinner was over retired thither again, until the time for resuming his "visits." It was the same before supper while the table was being got ready. After supper he returned to his study and did not finally retire until 11 o'clock, by which time heaviness came on, and drove him to go up to sleep. This was his way of work and life for more than thirty years. Through all that time he kept up this programme of study. Amusement, whether of body or mind, he held as nothing in comparison with the study and practice of the art of medicine. There was no hour of his life which was not given to duty private or public, professional or domestic. If perchance he invited a guest to sup or to dine, he did not consider it wrong or discourteous to excuse himself soon after the meal, for the sake of his studies.—C. Sherrington, The Endeavour of Jean Fernel, New York, Cambridge University Press, 1946, pages 168-169.

BLADDER AND KIDNEYS

I say therefore that according to the opinion of the authorities the cause from which a stone arises in the bladder is a thick and viscous humor. And the indications by which it is manifested are many. For among these there is the fact that the urine issues from the bladder white and thin with sandy excrement, and with difficulty and severe pain in the pubic region; and a boy holds his yard with his hands and rubs it and works with it and often the yard is erect and the anus protrudes; and in drawing the hand over the bladder it feels hard.—The Surgery of Theodoric, vol. 2, books 3 and 4, translated by E. Campbell, M.D., and J. Colton, M.A., New York, Appleton-Century-Crofts, Inc., 1960, pp. 119-120.

THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

In a dramatic, last-minute effort to win some kind of Forand-type legislation in the current session of Congress, officials of the AFL-CIO have launched a scurrilous assault on the American Medical Association.

With little regard for the truth, its political education arm, COPE, has attacked the good name of the A. M. A., its 178,000 member-physicians, and its affiliated state and county medical associations.

In a political memorandum a list of sweeping charges has been circulated with the intention of showing that the A. M. A. historically has opposed beneficial health measures. The memorandum suggests that A. M. A. disapproval of Forand-type legislation is ridiculous and without merit.

Let me cite briefly a few of the COPE allegations.

The memo begins by contending that "a generation ago, the A. M. A. opposed the requirement that all cases of tuberculosis be reported to a public authority—the foundation for tuberculosis control methods." This accusation is completely unfounded. The A. M. A. actually has advocated the reporting of all cases of tuberculosis to a public authority since 1899 and as recently as 1944.

COPE then charges that the A. M. A. was against smallpox vaccination, immunization against diphtheria, venereal disease clinics, tuberculosis and cancer clinics, blood banks, Medicare, and various other items. It alleges that the A. M. A. has opposed, and fought, them all. The facts are these:

The A. M. A. has campaigned for compulsory smallpox vaccination since 1863.

The A. M. A. has cooperated with public health agencies for the prevention of contagious diseases for more than 80 years. It has never attacked provisions for immunization against diphtheria by public health agencies.

Official A. M. A. actions on venereal diseases can be traced back to 1874, and it is categorically untrue that the Association was against the creation of public venereal disease clinics.

The charge that the A. M. A. opposed the creation of free diagnostic centers for tuberculosis and cancer also is utterly without foundation. Our cooperation in these matters is a recorded fact.

The allegation that the A. M. A. fought the Red Cross plan to set up a nationwide reserve of civilian blood banks is a gross distortion of the truth. While we may have differed on method, we supported the objectives—immediately and completely. Furthermore, I add this personal note: Nine years prior to the Red Cross efforts my wife and I made possible the establishment of the fourth blood bank in America and the first in Florida.

COPE implies that the A. M. A. opposed government medical care to dependents of men in the armed forces. The facts are that the A. M. A. did not oppose Medicare. In fact, the House of Delegates when expounding its policy on Medicare specifically stated "the policy advocated should not in any way be construed as one of opposition by the A. M. A. to dependent medical care . . . the position recommended refers only to the manner it should be provided, for it is determined by Congress to be a proper emolument of military service."

Contrary to COPE, the A. M. A. is busy every day of the year in hundreds of projects for the public and for medical science. It continuously emphasizes and promotes all positive programs in behalf of the American public. For an influential labor organization, and its "educational" arm, to attempt to destroy the American public's confidence in the world's greatest medical organization is most contemptible.

Louis M. Orr, M.D.
Orlando, Fla.

ORGANIZATION SECTION

THE NEW MEDICAL DISCIPLINARY COMMITTEE

In February, 1959, the Board of Trustees formed a new committee to inquire into the status of medical discipline in the United States. Dr. Raymond McKeown, a member of the Board, was named Chairman of the new Committee and appointed as members were Drs. James H. Berge, Paul G. Henley, H. Thomas McGuire, and E. G. Shelley.

The Committee soon felt the need for consultation with persons experienced in matters of medical discipline and two such men have accepted appointments to aid the Committee. They are Dr. Stiles D. Ezell, associate secretary of the federation of state licensing boards, and Dr. Harold E. Jervey Jr., the federation's president-elect. At the most recent meeting of the Board of Trustees, Dr. Louis A. Buie was named to the Committee.

The Committee is authorized to investigate, with the assistance of the Law Division, the adequacy of disciplinary rules, laws, and procedures as applied to medical practice and licensure and medical society membership, and the degree to which efficient discipline is maintained among medical practitioners, in the interests of the public and the medical profession.

Initial Activities

In pursuit of these objectives, the Committee has agreed on the following activities: (1) To examine the standards, procedures, and rules of medical societies and boards which deal with professional discipline and to evaluate the adequacy of the existing systems of medical discipline within the perspective of practical, ethical, and legal considerations. (2) To summarize and evaluate existing state laws and medical licensure board regulations affecting medical discipline; the adequacy of such laws and regulations; and the extent to which state licensure boards are equipped to or do maintain satisfactory medical discipline through revocation or suspension of medical licenses. (3) To study the extent to which discipline is maintained by medical staffs in hospitals throughout the United States. (4) To determine whether the A. M. A. could or should become more active in guidance and participation in matters relating to medical discipline; and, if an affirmative finding is made, to recommend the establishment of appropriate mechanisms and procedures to carry out such participation efficiently. (5) To conduct fact-finding surveys and field investigations, through regional or sectional studies, as a basis for reporting on the problems relating to medical discipline and recommending appropriate measures to improve the over-all mechanism of equitable medical discipline in the interests of the public and the profession; and (6) To recommend and draft, if necessary, on the basis of results of thorough studies and investigations, new legislation or amendments to existing legislation or to recommend, if necessary, additional procedures for medical societies in order that the quality of patient care may be improved by maintaining adequate standards of medical discipline.

Medical Disciplinary Committee Report

Three separate but related courses of action have been instituted by the Committee in the course of its year's activity in this field.

First, it has polled by mail the executive secretaries of all the state and some of the larger county medical societies as well as the secretaries of all state boards of medical examiners for opinions and suggestions relative to its area of interest.

Second, it has initiated a series of personal visits by members of the staff of the Law Division to state medical society and licensure board officials who are close to the matter of discipline.

And last, the Committee has so located its meetings geographically that it has been able to meet with representatives of regional areas in communal discussion of matters relating to medical discipline. Two such meetings have been held to date; the first was in Denver on July 24 and the second in Atlanta on Nov. 16. More are planned for the future.

Special Interests

In addition to its primary interests (to ascertain if disciplinary procedures exist and are used) a secondary Committee interest in certain ethical and legal matters has developed. Some of these were suggested by the members themselves at the organizational session; others were developed in the regional discussions. They include:

—The allegation that some physicians overcharge insurance companies or perpetrate fraud in the presentation of insurance claims.

—The allegation that proper disciplinary procedures do not follow convictions of physicians for various crimes, criminal negligence in practice, and gross incompetence.

—The contention that state boards of medical examiners have neither the funds nor the staff to investigate complaints against physicians properly.

–The belief that liaison between state boards is often faulty or lacking in the transmission of information on the suspension or revocation of licenses.

Although the Committee has mailed queries to many state and county society officials as well as secretaries of examining boards, it feels that personal contact will provide better insight into the problems that exist. Conducting regional sessions with invited guests is one method being used to provide this personal approach. Another is the series of state visits being undertaken by members of the staff of the Law Division. About one-fifth of the states have been visited to date.

Despite its other investigative operations, the Medical Disciplinary Committee is also anxious to hear from individual physicians who would like to make comments or recommendations concerning the Committee's work. Such comments should be sent to the Committee's secretary, Mr. C. Joseph Stetler, 535 N. Dearborn St., Chicago 10. The Chairman has pointed out, however, that the Committee is interested in individual cases only as they illustrate malfunctions of present procedures or point up a breach in disciplinary coverage. The Committee has neither the authority nor the desire to adjudicate specific problems in the disciplinary field.

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

FOREIGN MEDICAL GRADUATES OTHER THAN INTERNS AND RESIDENTS

The present policy of the Council on Medical Education and Hospitals and the American Hospital Association regarding Educational Council for Foreign Medical Graduates (ECFMG) certification for foreign medical graduates serving as interns or residents is based on a fundamental concern for the welfare of patients. Any foreign medical graduate engaging in patient-care activities should be expected to demonstrate acceptable professional qualifications even though not appointed formally as an intern or a resident in a program under the purview of this Council.

Those physicians engaged in whole or in part in programs approved as internships or residencies will be considered as interns or residents even though appointed for administrative purposes as fellows, trainees, or by other title.

Those special training opportunities beyond the internship which exist mostly in university hospitals as distinctly separate programs from residencies are not subject to Council review or approval; however, such experience is often creditable toward specialty board certification. Eligibility for certification at a future date may hinge upon the ECFMG certification of the individual foreign medical graduate, even though the training was otherwise acceptable to a specialty board.

Directors of individual programs as well as administrators of national or local foundations, organizations, and agencies which award training or research grants to foreign medical graduates are morally responsible for assuring that such trainees, if engaging in patient-care activities in hospitals or clinics, have been qualified by ECFMG certification.

GOVERNMENT SERVICES

PUBLIC HEALTH SERVICE

Ad Hoc Committee.—An ad hoc committee was appointed to develop principles for community-wide health facility planning. It is sponsored by the Public Health Service and the American Hospital Association, and will be headed by Mr. George Bugbee, president of the Health Information Foundation, New York City. One of the principal functions of the committee will be to establish authoritative guide lines for area planning groups in developing plans for improved hospital services and facilities, especially in metropolitan areas. Other major objectives set for the committee are the development of principles to be followed in the organization and composition of area planning groups and steps which should be taken to assure the acceptance of a planning organization as the authoritative central hospital planning agency of the community. According to PHS Surgeon General Leroy Burney the development of more hospital planning groups is essential if we are to make progress in solving the many problems now facing hospitals, particularly in the urban and metropolitan areas. Some of these problems include spiraling hospital costs and the growing obsolescence of older institutions.

Members of the committee, in addition to Mr. Bugbee, are Mr. J. Milo Anderson, administrator, Strong Memorial Hospital, University of Rochester, Rochester, N. Y.; Mr. Ray E. Brown, superintendent, University of Chicago Clinics, Chicago; Mr. Gordon Cumming, chief of the bureau of hospitals, California Department of Public Health, Berkeley, Calif.; Dr. Jack C. Haldeman, assistant surgeon general and chief, division of hospital and medical facilities, Public Health Service; Mr. John R. Mannix, executive vice-president, Blue Cross of Northeast Ohio, Cleveland, Ohio; Dr. Rayden C. Nicholson, executive director, Hospital Council of Greater New York, New York; Mr. Vincent Otis, director, division of hospital and related services, Wisconsin State Board of Health, Madison, Wis.; Mr. Delbert L. Pugh, executive director, Columbus Hospital Federation, Columbus, Ohio; Mr. Hiram Sibley, secretary, council on planning, financing, and prepayment, American Hospital Association, Chicago; Mr. Paul Snelson, director, hospital division, Oklahoma Department of Health, Oklahoma City; Mr. James J. Souder, project director, collaborative research in hospital planning, New York City; Dr. Ray E. Trussell, executive director, School of Public Health and Administrative Medicine, Columbia University, New York City; Dr. David B. Wilson, director, University Hospital, University of Mississippi, Jackson, Miss.; and Dr. Willard A. Wright, Chairman, Committee on Medical and Related Facilities, American Medical Association, Williston, N. D.

Quarantine Procedures.—Quarantine procedures at international airports have been simplified. The principal change is elimination of preliminary group clearance. Under the new procedures, if the aircraft captain certifies that no illness has been observed during flight, only individual clearance of passengers is required. Prior to adoption of these new procedures, both group clearance and individual clearance were required. Group clearance had been maintained to prevent spread of disease by travelers who may have symptoms of quarantinable illness on arrival. If such illness is reported aboard a plane, or there is an unusual disease problem in the country where the flight originates, the strictest quarantine procedures will be applied. The only major airport where passengers will be kept in groups is Miami, Fla., where the means of access to quarantine facilities makes the change impractical. Additional streamlining of quarantine procedures is being made wherever possible. The new procedures stress the responsibility of travelers for maintaining valid immunization records and the responsibility of airlines for reporting illness observed among passengers.

In preparation for travel abroad where a passport is required, prospective passengers receive the form for the international certificates of vaccination with the passport application. This form may also be obtained from travel agencies, transportation companies, local and state health departments, and offices of the Public Health Service, Department of Health, Education, and Welfare.

Sanitary Requirements.—Ships on the Great Lakes and St. Lawrence Seaway will be prohibited from polluting the water supplies of port communities by a ruling which requires ships either to avoid the areas from which communities draw their water supplies or to adopt specific safeguards against pollution. Community water purification systems are geared to deal with a uniform flow of pollutants. Any sudden and unexpected increase in pollutants could overload the system and some impurities might get into the drinking water supply before corrective measures could be taken. With more vessels using these waterways (tonnage increased about 80% in the seaway's first season) this could easily occur. Each ship captain, on entering the seaway at Montreal, will be given charts of the delimited areas of all the ports on his route. Ships entering these delimited areas must follow one of several methods of controlling pollution while there. They can (1) treat their waste material by an approved sewage treatment device, (2) store it in suitable retention tanks until they leave the area, (3) empty it into the port's sanitary sewer system, (4) adopt any other method of handling their waste which meets the approval of both the local authorities and the Public Health Service, and (5) unload garbage on the dock only if there are adequate facilities for handling it.

Vital Statistics.—Heart disease, cancer, apoplectic strokes, and accidents accounted for 71% of all deaths in 1958, according to the Office of Vital Statistics. The 1,647,886 deaths that occurred in 1958 gave the nation a death rate of 9.5 per 1,000 population, compared to a rate of 9.6 in 1957. The death rates for heart disease and cancer in 1958, 367.9 and 146.9 respectively, were slightly lower than the comparable rates in 1957, 369.6 and 148.7. The rate for vascular lesions remained about the same. The death rate for accidents, 52.3, was almost 7% lower than the rate of 56.0 in 1957. Chiefly as a result of the influenza epidemic of 1957-1958, the toll of deaths from influenza and pneumonia remained high in 1958—57,439 deaths, or a death rate of 33.2 per 100,000 population. The death rate for these conditions in 1958, the second highest in 10 years, was more than 7% lower than the rate of 35.8 recorded in 1957.

MEDICAL NEWS

COLORADO

Change of Address.—Effective Feb. 15, the new address of the Colorado State Department of Public Welfare is as follows: Colorado State Department of Public Welfare, State Services Building, 1525 Sherman St., Denver 3. Attention: Library.

Anesthesiologists Establish Student Award.—The Colorado Society of Anesthesiologists at the annual meeting of Feb. 20 elected the following officers for the coming year: president, Dr. Norma B. Bowles, Colorado Springs; vice-president, Dr. Rex D. Nash, Colorado Springs; president-elect, Dr. John C. McAfee, Denver; secretary-treasurer, Dr. Charles B. McCrory, 385 Forest St., Denver 20; assistant secretary-treasurer, Dr. Donald W. Stein, Denver. At this same meeting the society voted to establish an award at the University of Colorado School of Medicine for the senior student showing "outstanding interest in the field of anesthesia." The award is to be given at the annual awards convocation and is to be known as the C. Walter Metz Award of the Colorado Society of Anesthesiologists.

ILLINOIS

Changes in Admission Requirements.—Three changes in requirements for admission to the University of Illinois College of Medicine have been approved by the board of trustees. One change is that the prospective medical student will be required to follow a sequence of study in one subject matter area. Also, the student will have to present 94 semester hours for admission instead of the current 88. These six additional hours are to be in advanced courses toward which the student must work during his first two years as an undergraduate. The final change involves the study of nuclear physics as part of an already current physics requirement. The six-hour sequence does not have to be in a scientific area. The student will have a free hand in choosing his area of study. These changes become effective in September, 1962.

Chicago

Dr. Thorek Named Editor.—Dr. Philip Thorek, Chicago, was named editor-in-chief of the *Journal of the International College of Surgeons*. Dr. Thorek succeeds his father, the late Dr. Max Thorek, founder of the college.

Northwestern Alumni Reunions.—The annual Medical Faculty Alumni Reunion dinner of Northwestern University Medical School will be held May 14 at the Furniture Club of America, 666 Lake Shore Dr., Chicago. The social hour will start at 6 p. m. and dinner will be served at 7 p. m. A skit will be presented by the medical students as entertainment at the dinner. Reservations at $8 a person may be made at the Medical Alumni Office of Northwestern Medical School, 303 E. Chicago Ave., Chicago 11, not later than May 11. During the convention of the American Medical Association in Miami Beach, alumni of Northwestern Medical School will hold their annual luncheon on June 14 in the Imperial Room of the Roney-Plaza Hotel at 12:30 p. m. Tickets ($3.50) are available from the Medical Alumni Office.

MASSACHUSETTS

Harvard Pathologist Honored.—The second honorary doctoral degree to be awarded by the National University of Nicaragua in Leon was presented to Dr. Franz C. von Lichtenberg, of the Harvard Medical School and the Peter Bent Brigham Hospital, Boston. During the summer of 1959, Dr. von Lichtenberg worked in Nicaragua through an educational exchange grant awarded him under the Smith-Mundt Act. He is an associate in pathology at Harvard. While in Nicaragua he was visiting lecturer of medicine (pathology) at the National University of Nicaragua, was a consultant in the organization of the University Pathology Laboratory at San Vicente Hospital in Leon, and assisted in developing an Outpatient Department and Public Health Center at the university. Dr. von Lichtenberg received the degree of doctor honoris causa.

Hungarian Microbiologist Named Visiting Lecturer.—Dr. George Ivanovics, professor of microbiology, Medical University, Szeged, Hungary, was appointed a visiting lecturer in the department of bacteriology and immunology, Harvard Medical School, Boston, serving through May 31. While at Harvard, Dr. Ivanovics will conduct informal seminars in the department of bacteriology and immunology and will carry on his research in microbiology in the laboratory of Dr. Bernard D. Davis, head of the department. He will also lecture in other departments of the university. During his stay in the United States, Dr. Ivanovics plans to visit several other medical institutions. In 1948

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

again in 1952 Dr. Ivanovics was awarded the Hungarian National Prize (Kossuth Prize) for his microbiological research.

MICHIGAN

Course in Hospital Housekeeping.—A course in hospital housekeeping will be given April 4-May 26 for the 12th consecutive year at Michigan State University, East Lansing. The course is sponsored by the American Hospital Association in cooperation with the university. It will provide practical training in hospital housekeeping procedures for executive housekeepers, members of hospital housekeeping staffs, and prospective employees. Enrolment will be limited to 40 students. The course will include the philosophy of hospital care and institutional organization, personnel management, institutional management, housekeeping supplies, equipment, and procedure. For information, write the American Hospital Association, 840 N. Lake Shore Dr., Chicago 11.

MISSOURI

Annual Lecture.—Dr. J. Hartwell Harrison, clinical professor of genitourinary surgery, Harvard Medical School, Boston, will deliver the 10th annual Memorial Lecture at the Menorah Medical Center of Kansas City, Tuesday, April 26. The subject will be "The Present Status of Renal Transplantation," and the time, 8 p. m.

NEBRASKA

Plan Library for Medicine and Pharmacy Schools.—Creighton University Schools of Medicine and Pharmacy will soon have a new integrated library, according to the Very Rev. Carl M. Reinert, S. J., Creighton president. The university has purchased the building at 1401 Davenport St., located directly across from the two Creighton schools. Father Reinert asserted that purchase of this property in no way affects selection of a site for proposed construction of a new Creighton Medical Center in the future. The building was acquired at this time "to satisfy a need for additional space caused by rapid expansion" of the Creighton Library collection in pharmacy and medicine. This building will replace two large rooms located on separate floors in the Medical School building. Libraries of the two schools will be integrated into one unit. Main reading room in the new Medicine-Pharmacy Library will utilize fluorescent lighting. Separate rooms will house the periodicals and rare books collections. In addition the building includes four rooms for private offices and work rooms, plus seven fireproof vaults for storage.

Personal.—Dr. Robert C. Rosenlof was named to the full-time internal medicine faculty at the University of Nebraska College of Medicine, Omaha. Dr. Rosenlof has been in private practice in Kearney since his discharge from the Air Force in 1958.—Dr. John G. Freeman, former clinical director and for a time acting superintendent of the Jamestown (N. D.) State Hospital, was named assistant professor of neurology and psychiatry at the University of Nebraska College of Medicine and research psychiatrist at the Nebraska Psychiatric Institute at Omaha. In the latter position, Dr. Freeman has charge of a 10-bed research unit devoted to teaching and research in connection with patients admitted from any of the three state hospitals in Nebraska.

NEW JERSEY

Day School Program for Retarded Children.—The Training School at Vineland has a new day school program for mentally retarded children in the Southern New Jersey area, Dr. Walter L. Jacob, director of the school, announced. The new program is for nonresidential children and joins other outpatient clinic services of the school. It ranges from nursery classes for the very young child, to vocational training for the young adult. The first 6 to 12 weeks of a child's enrollment will serve as a trial period. During this time the child will be evaluated in terms of social, emotional, and academic status to determine the type of program deemed most suitable. If the program can be provided, the child will be accepted for continued training. Morning and afternoon classroom sessions will be available. Parents will be responsible for transportation to and from the training school. For information, write The Registrar, Day School Program, The Training School at Vineland, N. J.

TEXAS

Annual Meeting in Fort Worth.—The Texas Medical Association will hold its 1960 annual session in Fort Worth, April 9-12. Twenty-six guest speakers will be featured. Dr. Louis M. Orr, President, American Medical Association, will be the speaker at a general session luncheon on Monday, April 11, and Dr. John R. Heller, of Bethesda, Md., assistant surgeon general, U. S. Public Health Service, will be the main speaker for the luncheon the following day. The program will include two general sessions, nine section meetings, 13 refresher courses, and a daily film program. In addition, about 100 papers will be presented by Texas physicians during the three full days of scientific program. Exhibits will be shown by 90 commercial firms and 35 scientific exhibits will be presented. Over 20 related medical specialty groups will meet. The president's party will be held April 12. A sports program is arranged, including a golf tournament, sailing and boating, handball, swimming, tennis, and skeet shooting. For information, write the Texas Medical Association, 1801 N. Lamar Blvd., Austin, Texas.

VERMONT

Doctorate Program in Biophysics Approved.—A new Ph.D. program in physiology and biophysics was approved by the University of Vermont College of Medicine trustees. This is the third Ph.D. program to be approved and started in the last three years. The first two were in biochemistry and pharmacology. Biochemistry is a joint program of the College of Medicine and the College of Agriculture.

Loan Fund for Students.—Dr. G. Stedman Huard, Pasadena, Calif., a 1946 graduate of the University of Vermont College of Medicine, Burlington, and a native of Winooski, has established a $25,000 loan fund for university medical students. Establishing the fund with a gift of $5,000, Dr. Huard will add $20,000 over the next four years, making a total of $25,000 available by 1961. Under the terms of the fund, special consideration is to be given students in the third and fourth years of medical school and to students from Winooski and the State of Vermont. Loans will be awarded by the university's committee on student aid, on the recommendation of the dean.

GENERAL

Request for Ophthalmology and Otolaryngology Papers.—The section of ophthalmology and otolaryngology of the Southern Medical Association announced that they are accepting papers by physicians of either specialty living in the area of the association for consideration for presentation at the next annual meeting in St. Louis Oct. 31-Nov. 3. The paper or an abstract of the paper may be sent to the Secretary, Dr. Albert C. Esposito, Suite 1212, First Huntington National Bank Building, Huntington, W. Va., as soon as possible.

Congress on Physical Medicine.—The third International Congress of Physical Medicine will be held Aug. 21-26 at The Mayflower, Washington, D. C. The preliminary prospectus covering the international conference carries information on registration, application to present a paper, a scientific exhibit, a scientific film, etc. A copy of this preliminary program may be had on request by writing Dorothea C. Augustin, Executive Secretary, Third International Congress of Physical Medicine, 30 N. Michigan Ave., Chicago 2.

Allergy Symposium in Barcelona.—An International Symposium on Allergy, organized by the European Academy of Allergy in collaboration with the Spanish Society of Allergy, will be held in Barcelona, Spain, June 3-4. Subjects for the program include (a) evaluation of the diagnostic methods used in allergy and (b) functional exploration of the respiratory and cardiovascular systems in asthma, emphysema, and allied conditions. For information, write to the secretary: Mr. Camps, Academia de Ciencias Medicas, Via Layetana 31, Barcelona 3, Spain.

Prize for Essay on Surgery.—The Samuel D. Gross Fund Prize will be awarded at the end of this year by the Philadelphia Academy of Surgery. The prize, $1,500, will be paid to the writer of the "best original essay" not exceeding 150 printed pages, octavo in length, illustrative of some subject in surgical pathology or surgical practice founded on original investigation. The author must be an American citizen. All manuscripts should be submitted no later than Sept. 1 to Dr. George P. Rosemond, Chairman, Samuel D. Gross Fund, 3401 N. Broad St., Philadelphia 40.

Truth Drugs.—A Yale psychiatrist warns that the so-called "truth drugs" often produce untruthful statements from the patient and are therefore not reliable for criminal interrogation. Dr. Lawrence Z. Freedman, of the Yale School of Medicine, New Haven, Conn., emphasizes that sodium amobarbital and thiopental sodium are extremely useful in psychiatric treatment, but that the "truth" factor has been misinterpreted by the public. Narcoanalysis, the technique of using drugs to stimulate the patient's talk, will usually stimulate the noncommunicative patient to talk uninhibitedly and thus speed treatment, but the talk is not always the truth.

Psychosomatic Meeting in Montreal.—The annual meeting of the American Psychosomatic Society will be held March 25-27 at the Sheraton–Mt. Royal Hotel, Montreal. The program includes 25 papers. Dr. Eric D. Wittkower, associate professor of psychiatry, McGill University, Montreal, will give the presidential address the morning of March 27, after which a panel discussion, "Contributions of Behavioral Scientists to Psychosomatic Medicine," will be moderated by Dr. Wittkower. A business meeting will be held the afternoon of March 26. For information, write Dr. Eugene Meyer, 265 Nassau Road, Roosevelt, N. Y., Secretary-Treasurer.

Conference on Thrombolytic Agents.—On April 8-9 a Conference on Thrombolytic Agents, sponsored by the Hematology Study Section, will be held in Chicago. The conference will be concerned with the clinical application of thrombolytic agents, laboratory control of therapy, and standardization of agents. There will also be an assessment of the basic knowledge of the fibrinolytic system, including the purification of profibrinolysin and the action of activators and inhibitors. Speakers will include American and foreign investigators. Workers active in the field may obtain information about attendance from Dr. Kenneth M. Brinkhous, Department of Pathology, University of North Carolina, Chapel Hill, N. C.

New Fifty Year Club.—Dr. John H. McCurry, of Cash, Ark., is interested in forming an A. M. A. Fifty Year Club in which membership would be limited to members of the Association who have been in practice 50 years or more. The first meeting of the new club is expected to be held during the annual clinical meeting of the Association in Washington, D. C., in November, 1960. Those who are qualified and desire to join this organization are requested to so advise Dr. McCurry, giving their complete name and address. Dr. McCurry plans to be in Miami at the June meeting to begin organizational procedures and to see any who qualify at this meeting.

Meeting on Medical Television.—The Council on Medical Television, an organization concerned with the uses of television in the health science professions, will hold its second meeting on April 20-21 at the Clinical Center, National Institutes of Health, Bethesda, Md. This meeting, will have as its theme "Pedagogic Techniques in Televised Medical Education." Examples of techniques currently used in medical schools and institutions with television facilities will be demonstrated and discussed. Attendance is limited to council members and invited observers. For information, write Mr. John K. MacKenzie, Executive Secretary, Council on Medical Television, 33 E. 68th St., New York 21.

Meeting on Nuclear Medicine in San Antonio.—The Southwestern Society of Nuclear Medicine will hold its fifth annual meeting March 26-27 at the Menger Hotel, San Antonio, Texas. Dr. Peter E. Russo, Oklahoma City, president of the society, will open the meeting with an address. Twelve papers are scheduled, each to be followed by a discussion period. Two panel discussions will be held with the following titles and moderators: "Responsibilities of the Physician and Institution Using Radiation," Dr. Vincent P. Collins, Houston, Texas, and "Value of Isotopes in Hematology," Dr. William C. Levin, Galveston, Texas. For information, write Dr. James R. Maxfield Jr., 2711 Oak Lawn Ave., Dallas 19, Texas, Secretary and Treasurer.

Meeting of Anatomists in New York City.—The seventh International Congress of Anatomists and 73rd annual meeting of the American Association of Anatomists will be held at the Statler Hilton Hotel, New York City, April 11-16. Over 600 papers will be presented, and four symposiums have been organized on the following subjects:

The Structure of the Eye.
Microcirculatory: Pituitary and Bone Marrow.
Fine Structure.
Anatomy and Biomechanics.

Delegates from over 30 foreign countries will participate. Registrants from the United States and Canada will be assessed a registration fee. For information, write Dr. Oliver P. Jones, Program Secretary, Department of Anatomy, University of Buffalo, Buffalo 14, N. Y.

Orthoptic Council Examinations.—The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in August and October. The written examination will be nonassembled and will take place on Thursday, Aug. 18, in certain assigned cities and will be proctored by designated ophthalmologists. The oral and practical examinations will be on Saturday, Oct. 8, in Chicago preceding the meeting of the American Academy of Ophthalmology and Otolaryngology. Applications for examination will be received by the office of the Chairman of Examinations, Dr. Frank D. Costenbader, 1605 22nd St., N. W., Washington 8, D. C., and must be accompanied by the examination fee of $30. Applications will not be accepted after July 1.

Gastroenterology Groups Meeting in New Orleans.—The 61st annual meeting of the American Gastroenterological Association will be held April 1-2 at the Roosevelt Hotel, New Orleans. On March 30 the American Gastroscopic Society will hold its 19th annual meeting, and on March 31 the Gastroenterological Research Forum and the Gastroenterology Research Group will meet at the Roosevelt Hotel. The program for the American Gastroenterological Association is organized under the following major headings:

Peptic Ulcer.
Pancreas.
Exudative Gastroenteropathy.
Colon.
Small Intestine.
Gastric Cancer.
Postgastrectomy Steatorrhea.
Liver.
General.

The President's Address, "Our Responsibility to World Gastroenterology," will be given by Dr. H. Marvin Pollard, Ann Arbor, Mich., the morning of April 2, followed by the sixth annual Memorial Lecture of the association, "Causative Factors in Gastrointestinal Cancer," by Dr. G. Burroughs Mider, Bethesda, Md. Over 85 papers are scheduled. At the annual banquet, April 1, the Julius Friendenwald Medal will be presented to Dr. Chester M. Jones, Boston. For information, write Dr. Wade Volwiler, University of Washington School of Medicine, Seattle 5, Secretary.

Annual Dermatological Meeting.—The American Dermatological Association, Inc., will hold its 80th annual meeting April 8-12 at the Boca Raton Hotel and Club, Boca Raton, Fla. Dr. Marion B. Sulzberger, New York City, will give the presidential address, "Education for Dermatology in the United States," to open the first scientific session the morning of April 8. The program includes more than 25 papers, with following discussions. Election of officers will take place the morning of April 9. An awards session, April 12, will be followed by a noon luncheon meeting of the board of directors and the American Dermatological Association Research & Educational Fund, Inc. The 1961 meeting of the association will be held at the Castle Harbour Hotel, Tucker's Town, Bermuda. For information, write Dr. Wiley M. Sams, 308 Ingraham Bldg., Miami 32, Fla., Secretary.

Report on Heart Research Support.—Sums allotted to scientific research by the American Heart Association and its affiliates since its reorganization as a voluntary health agency in 1948 have approached 50 million dollars, according to the association's annual report. The 1959 Heart Fund drive raised $24,004,865, a total more than nine times the sum contributed in the association's first campaign in 1949. In reviewing the association's program, the annual report notes that community service programs have been developed, including work evaluation units to aid the heart patient in returning to work, programs for prevention of rheumatic fever, vocational guidance for cardiac-handicapped youth, assistance to families in rehabilitation of stroke patients, counseling to help patients follow prescribed diets, work simplification classes to show cardiac homemakers how to "take it easy," and information and referral services.

Scholarship for Health Museum Study.—Applications are being accepted for the 1960 Lester Taylor Scholarship of the Cleveland Health Museum, Dr. Bruno Gebhard, museum director, announced. The $500 scholarship is open to graduate students (having A.B., R.N., or equivalent) interested in health or museum education. The winner spends 6 to 12 weeks at the Health Museum studying visual techniques in education, under direction of the staff. The period of year is at the option of the candidate. The student selects a project suited to his needs and interests and submits a written report at the end of his internship. The scholarship is made available by the Women's Committee of the Cleveland Health Museum in honor of the Museum's first president. A tuition fee of $100 will be paid from the $500 stipend. The remainder is paid directly to the candidate for living expenses. Address requests to Dr. Bruno Gebhard, Director, Cleveland Health Museum, 8911 Euclid Ave., Cleveland 6.

American Board of Medical Hypnosis.[*]—The American Board of Medical Hypnosis will certify between Jan. 1, 1960, and June 30, 1960, those physicians who meet the following standards: (1) prior certification by one of the A. M. A. approved American Medical Specialty Boards, and (2) documented evidence, acceptable to the American Board of Medical Hypnosis, of seven years' experience with medical hypnosis as part of the practice of their basic specialties. In the case of general physicians, active membership in the American Academy of General Practice will be accepted in lieu of A. M. A. Specialty Board Certification. During this six-month period it will not be necessary for applicants to pass special examinations for this board, provided that the aforementioned requirements are satisfactorily fulfilled.

[*] Editor's Note: The American Board of Medical Hypnosis has not been approved by either the A. M. A. Council on Medical Education and Hospitals or by the Advisory Board for Medical Specialties. It is, therefore, not recognized by the A. M. A. as a regular medical specialty board.

International Symposium on Congenital Heart Disease.—The second International Symposium of the Deborah Hospital on "Current Concept in Medicine" will be held April 28-30 at the Bellevue Stratford Hotel, Philadelphia, on congenital heart disease. This is the second of a series of symposiums which attempt to present changing concepts regarding various types of thoracic disease. Sessions are scheduled under the following titles:

Pathogenetic Factors in Congenital Heart Disease.
Definitive Diagnosis of Congenital Heart Disease.
The Fate of the Child with Unrelieved Congenital Heart Disease.
Surgical Tools.
Special Surgical Considerations.
Surgery of Congenital Heart Disease.
Management of the Cyanotic Newborn.

Twelve fireside conferences are scheduled for the evening of April 28. There is no registration fee. For information, write Dr. Paul K. Bornstein, Northwest Corner, 9th and Walnut Streets, Philadelphia 7.

Dr. Plimpton Named President of Amherst.—Dr. Calvin H. Plimpton, associate professor of clinical medicine at Columbia University College of Physicians and Surgeons, New York City, will succeed Charles W. Cole, Ph.D., as president of Amherst College, Amherst, Mass. Dr. Cole is retiring in June to join the Rockefeller Foundation. In 1946 Dr. Cole left his post as professor of history at Columbia to become 12th president of Amherst. The 139-year-old New England institution's 13th president is also a Columbia alumnus. The university awarded Dr. Plimpton a doctor of medical science degree in 1951. Both men received their undergraduate degrees at Amherst. Dr. Plimpton, who joined the faculty of Columbia's College of Physicians and Surgeons in 1949, also serves as assistant dean of the medical school. He is assistant attending physician at Presbyterian Hospital in the Columbia-Presbyterian Medical Center. He has served on the admissions committee of the college of Physicians and Surgeons since 1950. In its 205-

year history, Columbia has produced among its alumni and staff more than 100 college and university presidents.

Railway Surgeons Meeting in Chicago.—The American Association of Railway Surgeons will hold their 72nd annual meeting in conjunction with the Surgeons of the Burlington Railroad April 7-9 at the Drake Hotel, Chicago, under the presidency of Dr. James S. Bell, of York, Neb. Two panel discussions are planned with the following titles and moderators: "Low Back Pain and the Working Man," Dr. John J. Fahey, Chicago, and "Cancer—New Developments in Treatment," Dr. Danely P. Slaughter, Chicago. The program includes 13 papers and the following movies:

Acute Gall Bladder Disease, Dr. Allen M. Boyden, Portland, Ore.
Flexion Exercises in Low Back Mechanical Disorders, Dr. Eugene M. Regen, Nashville, Tenn.
Staphylococcal Infections in Surgery, Dr. H. Rocke Robertson, Vancouver, B. C.

Technical exhibits are arranged. Dr. Bell will serve as toastmaster at the annual dinner the evening of April 8. The program is acceptable for 16½ hours of category II credit for members of the American Academy of General Practice. All physicians are invited. There is no registration fee. For information, write Dr. Chester C. Guy, 5800 Stony Island Ave., Chicago 37, Secretary.

Accelerate Campaign Against Tuberculosis.—A plan to speed up the campaign against tuberculosis was announced March 1 by Dr. H. McLeod Riggins, New York City, president of the National Tuberculosis Association. The plan has been approved both by the board of directors of the NTA and by the executive committee of its medical section, the American Trudeau Society. Essentially, the plan is to use available antituberculosis drugs to eliminate all sources of tuberculosis infection by the adequate treatment of every person with active tuberculosis, and also selected persons with inactive disease. "We estimate that there are at least 250,000 active cases of tuberculosis in the United States today," Dr. Riggins said. "Of these, some 100,000 are not known to health departments. An additional 550,000 Americans are believed to have tuberculosis in an inactive form." In the stepped-up program to detect and treat all tuberculosis patients, the 2,700 state and local voluntary tuberculosis associations affiliated with the NTA will work in cooperation with state and local health departments. The eradication program adopted by the NTA grew out of a conference held at Arden House, Harriman, N. Y., recently, under the joint auspices of the Tuberculosis Program of the U. S. Public Health Service and the NTA.

Meeting on Internal Medicine.—The annual meeting of the American Society of Internal Medicine will be held April 1-3 at the Sheraton-Palace Hotel, San Francisco. Dr. Dwight L. Wilbur, San Francisco, past-president, American College of Physicians, will be the keynote speaker at the April 3 socioeconomic program session, entitled "The Practice of Internal Medicine Today-Tomorrow." Four speakers representing the individual practice of internal medicine, hospital administration, the pharmaceutical industry, and the office management field will follow. Dr. E. Vincent Askey, President-Elect, American Medical Association, will discuss problems of the aging at the opening session of the socioeconomic program April 2. Mr. Walter Barlow, executive vice-president of Opinion Research, will present a discussion on the development of a corporate image by the society and its component societies. The scientific responsibilities of a component society will be discussed by Dr. Howard F. Root, Boston, president, Massachusetts Society of Internal Medicine. Scientific exhibits and a ladies' program are arranged. On Saturday, April 9, the postconvention tour to Hawaii will begin. For information, write the American Society of Internal Medicine, 350 Post St., San Francisco 8.

Society News.—Officers of the **Western Association of Physicians** elected for the coming year are as follows: president, Dr. Clement A. Finch, Seattle; vice-president, Dr. Henry D. Brainerd, San Francisco; councillors, Dr. George E. Cartwright, Salt Lake City, and Dr. Robert J. Glaser, Denver. The following officers continue by reason of term of office: secretary-treasurer, Dr. Wade Volwiler, Department of Medicine, University of Washington, Seattle 5; councillors, Dr. Arthur W. Frisch, Portland, Ore., and Dr. John H. Lawrence, Berkeley, Calif.——Dr. George W. Dana, of New York City, was named executive director of **Southwestern Medical Foundation** in Dallas. Dr. Dana for the past two years has been director of North Shore Hospital in Manhasset on Long Island.——Dr. Francis W. Lynch, St. Paul, was elected president of the **American Academy of Dermatology and Syphilology**, succeeding Dr. Anthony C. Cipollaro, New York City. Dr. C. Fred Lehmann, of San Antonio, Texas, replaces Dr. Norman M. Wrong, Toronto, Canada, as vice-president. Dr. Robert R. Kierland, Rochester, Minn., Dr. Stanley E. Huff of Evanston, Ill., and Dr. Samuel J. Zakon, of Chicago, continue in their offices as secretary-treasurer, assistant secretary-treasurer, and historian, respectively. The next annual meeting of the academy will be at the Palmer House, Chicago, Dec. 3-8.

Report Increase of Young Fathers.—Statisticians of the Metropolitan Life Insurance Company report that young fathers in our country are "increasing rapidly in number." The number of children born in families where the husband is under 20 years of age rose from 40,000 to 106,000, or 165%, between 1940 and 1957. Although the relative increase in births diminishes with advance in age of the husband, it was 64% for husbands aged 30-34 years, and as much as 45% for those 40-44 years of age. Only in families where the husband is 55 years or older, have births failed to rise. During the 1940-1957 period, the number of American husbands at ages under 45 increased by almost one-third. Moreover, at the teen ages—where the sharpest rise in births has occurred—the number of married men has increased by about two-thirds. In 1957, births occurred at a rate of 598 per 1,000 in families where the husband was under 20 years of age; 3 out of 5 families with a teen-age husband had a child during the year. The proportion was about 2 in 5 in families where the husband was 20-24 years old, and well over 1 in 4 where he was 5 years older. The median age of the husband in families which had a child in 1957 was only 29.2 years; in 1940 the corresponding age was about 0.7 years higher. During 1957, families in which the husband was under 35 years of age contributed more than three-fourths of our newborn, whereas only one-tenth of the births were in families in which the husband was past age 40.

Population Growth in United States and Canada.—Statisticians of the Metropolitan Life Insurance Company reported that both the United States and Canada recorded large population gains during 1959. In the U. S., including Alaska and Hawaii, the increase exceeded 2,900,000, raising the total population of the states, including the Armed Forces overseas, to 179,250,000 at the end of the year. In the 9¾ years since the 1950 census more than 27.5 million people have been added to the population, an increase averaging 1.7% annually. Canada has been experiencing a higher rate of growth, the population having increased by 2.7% a year since the June, 1951, census. At the close of 1959 Canada's population reached 17,682,000 an increment of about 400,000 during the year and of almost 3,700,000 since June, 1951. Births in the U. S. have exceeded 4.1 million annually for six successive years. There were about 4,320,000 babies born in 1959, compared with the all-time high of 4,334,000 in 1957. In every year of the 1950's the birth rate was 24 per 1,000 or higher. General mortality in the United States declined slightly in 1959, the death rate decreasing to 9.4 per 1,000 population, from 9.5 in 1958. The rate for 1959 was only 2% above the all-time low of 9.2 per 1,000 in 1954. The number of births exceeded deaths by about 2,660,000 in 1959. In Canada during 1959 the birth rate was 27.9 per 1,000 population. The number of deaths totaled about 139,000, and the death rate was 8.0 per 1,000 population. The all-time low of 7.9 was established in 1958. Canada had a gain through migration in 1959, of about 50,000 persons. This was the smallest number for any year since 1951.

LATIN AMERICA

Tuberculosis Congress in Brazil.—The eighth Panamerican Congress on Tuberculosis, under the auspices of the Latin-American Union of Societies of Phthisiology, will be held under the presidency of Prof. Jose Silveira, of Brazil, July 10-16 at Cidade do Salvador, Bahia, Brazil. Official communications will include revision of value of epidemiology indices in tuberculosis and prognosis for tuberculous patients apparently cured. Symposiums are planned on the following subjects: B. C. G. in Latin America, present status of Abreugraphy in prophylaxis of tuberculosis, pulmonary mycosis, teaching of phthisiology, public health education, and publicity. Address all correspondence to M. Ezequiel Da Costa, Caixa Postal, 635, Bahia, Brazil.

FOREIGN

Charter Flight for Vienna Seminars.—The American Medical Society of Vienna, (Universitatsstrasse 11, Vienna I) has arranged a special charter flight for its members, to enable them to attend one of the seminar congresses which are held in Vienna Aug. 18 to Sept. 10. At a round-trip fare of $290, the plane will leave New York Aug. 11 for London and return from Paris Sept. 14. The stay in Europe will be on an individual basis. Several similar flights are being planned for 1961.

Conference on Electron Microscopy in Delft.—A European Regional Conference on Electron Microscopy will be held in Delft, Netherlands, Aug. 28-Sept. 3. The program will consider the following subjects: physics and technique of the electron microscope; image formation; ion-microscopy; preparation techniques; results of ultrastructure research in biology, medicine, chemistry, and metallography. Plenary and sectional meetings and colloquiums are planned. Contributors to plenary and sectional meetings should send an application form to the secretary of the organizing committee, A. L. Houwink, Lab. v. Microbiologie, Julianalaan 67A, Delft, Netherlands, and before May 1 should send in an outline of their paper, together with micrographs and a duplicate abstract of the paper. Contributors to the colloquiums should send in an application form and duplicate papers before June 15. Official languages of the congress are English, French, and German.

Conference on Congenital Malformations.—The International Conference on Congenital Malformations will be held in London July 18-22 under the sponsorship of the National Foundation. The meetings will take place in Church House and the headquarters hotel will be Grosvenor House. The honorary presidents of the conference include Sir Geoffrey Marshall, president, Royal Society of Medicine, and Mr. Basil O'Connor, president of the foundation. Prof. James D. Boyd, Cambridge University, will be the general chairman. The program will deal particularly with the incidence of congenital malformations and their relationship to social and medical conditions, the genetic and environmental factors that may be responsible, the normal mechanisms of embryogenesis and the conditions which result in abnormalities, the relationships between mother and fetus during pregnancy, and the obstetrical problems related to deformity. Investigators from more than 10 nations will participate. Information may be obtained by addressing the secretariat, Mr. Stanley E. Henwood, Executive Secretary, International Medical Congress, Ltd., 120 Broadway, New York City.

CORRECTION

Age Limit for Fellowships Is Thirty-five.—The executive secretary of the Helen Hay Whitney Foundation has written that in the item in the Medical News section of THE JOURNAL of Feb. 20, Volume 172, No. 8, page 829, reporting the availability of Helen Hay Whitney Research Fellowships, the age limit should have read 35 years not 25.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various locations, June 24. Final date for filing application was January 10. *Oral.* Miami Beach, April 25-30. Applications already on file. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

AMERICAN BOARD OF DERMATOLOGY: *Written.* Various locations, June 5, 1961. Final date for filing application is March 1, 1961. *Oral.* Philadelphia, Oct. 13-16. Sec., Dr. Beatrice M. Kesten, One Haven Ave., New York 32, New York.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* San Francisco, March 30-April 1; New York City, Nov. 14-17. Closing date for filing application: Jan. 2 and July 1. *Written.* Oct. 17. Closing date for filing application is May 1. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. St. Louis, April 10-12. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Part II, Oral and Clinical.* Chicago, April 11-16. Final date for filing application was August 1. Applications for certification in Part I, new and reopened, and requests for re-examination in Part II are now being accepted. Deadline for receipt of applications is August 1, 1960. After July 1, 1962 a minimum of three years of approved progressive residency training will be required. Training by preceptorship will no longer be acceptable. The initiation of preceptorships will not be approved after July 1, 1960. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* Jan. 23, 1961. Deadline for filing applications is July 1. *Oral.* San Francisco, May 9-13; Chicago, Oct. 3-7. Sec., Dr. Merrill J. King, Box 236 Cape Cottage Branch, Portland, Maine.

AMERICAN BOARD OF ORTHOPAEDIC Surgery: *Part I,* Nashville, Denver and Philadelphia, Apr. 13-14. Deadline for receipt of applications was Nov. 30. *Oral and Written, Part II.* Miami Beach, Jan. 3-5, 1961. Final date for filing application is July 1. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral,* Chicago, Oct. 3-6. Final date for filing application is April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: Memphis, April 21-23. Final date for filing application was March 7. *Examination in Forensic Pathology.* Memphis, April 22. Final date for filing application was March 7. Sec., Dr. Edward B. Smith, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Written.* New York City, January 1961. Final date for filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION: *Oral and Written.* New York, June 17-18. Sec., Dr. Earl C. Elkins, Mayo Clinic, Rochester, Minn.

AMERICAN BOARD OF PLASTIC SURGERY: *Oral and Written.* Milwaukee, May 1960. Final date for filing application was January 1. Corresponding Secretary, Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written, Parts I and III,* Philadelphia, Sept. 24. Final date for filing application is June 30. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York, New York, Dec. 12-13. *Child Psychiatry.* Chicago, April 25-26. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: *Examination.* Cincinnati, June 6-10; Dec. 5-9. Deadline for filing applications for the June examination was Jan. 1. Filing deadline for the December examination is July 1. A special examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Oral Examinations (Part II):* Kansas City, Kans., May 16-17, and Los Angeles, May 19-20. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

BOARD OF THORACIC SURGERY: *Oral.* May 1960. Final date for filing application was Dec. 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

AMERICAN BOARD OF UROLOGY: *Written.* December. *Oral-Clinical.* Chicago, February 1961. Exec. Sec., Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 26.

DEATHS

Armstrong, Thomas Morrell Ⓜ Philadelphia; University of Pennsylvania School of Medicine, Philadelphia, 1913; member of the Association of Life Insurance Medical Directors of America; veteran of World War I and was awarded the Croix de Guerre by the French government for meritorious service; medical director of the Philadelphia Life Insurance Company; died Dec. 31, aged 70, of diffuse obstructive emphysema.

Ashcraft, Virgil Lee, Reform, Ala.; University of Alabama School of Medicine, 1912; for many years secretary of the Pickens County Medical Society; director of the Bank of Reform; died Jan. 4, aged 73.

Baer, Walter Kreider Ⓜ Lancaster, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1905; formerly affiliated with the city bureau of health and school medical inspection service; on the staff of the Lancaster General Hospital, where he died Jan. 4, aged 79.

Barker, Joseph Michael Ⓜ Beverly Hills, Calif.; born in Washington, D. C., May 16, 1910; Georgetown University School of Medicine, Washington, D. C., 1939; interned at the Georgetown University Hospital in Washington, D. C., where he served a fellowship; served a fellowship at the University Hospital in Ann Arbor, Mich.; specialist certified by the American Board of Internal Medicine; certified by the National Board of Medical Examiners; fellow of the American College of Physicians; associate clinical professor of medicine at the University of California at Los Angeles School of Medicine; served on the faculty of his alma mater and the University of Southern California School of Medicine at Los Angeles; veteran of World War II; affiliated with St. John's Hospital, Santa Monica, Cedars of Lebanon Hospital, Hollywood Presbyterian Hospital, Queen of Angels Hospital, Mount Sinai Hospital, and St. Vincent's Hospital, all in Los Angeles; author of "The Unipolar Electrocardiogram"; died in Arlington, Va., Jan. 12, aged 49.

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Branaman, Ernest L., Taylorsville, Ky.; University of Louisville Medical Department, 1894; served as a member of the Spencer County Board of Health; died in the Guerrant Clinic and Hospital, Winchester, Jan. 3, aged 87.

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American Board of Anesthesiology: *Written.* Various locations, June 24. Final date for filing application was January 10. *Oral.* Miami Beach, April 25-30. Applications already on file. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

American Board of Dermatology: *Written.* Various locations, June 5, 1961. Final date for filing application is March 1, 1961. *Oral.* Philadelphia, Oct. 13-16. Sec., Dr. Beatrice M. Kesten, One Haven Ave., New York 32, New York.

American Board of Internal Medicine: *Oral.* San Francisco, March 30-April 1; New York City, Nov. 14-17. Closing date for filing application: Jan. 2 and July 1. *Written.* Oct. 17. Closing date for filing application is May 1. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

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American Board of Ophthalmology: *Written.* Jan. 23, 1961. Deadline for filing applications is July 1. *Oral.* San Francisco, May 9-13; Chicago, Oct. 3-7. Sec., Dr. Merrill J. King, Box 236 Cape Cottage Branch, Portland, Maine.

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American Board of Pediatrics: *Written.* New York City, January 1961. Final date for filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

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American Board of Plastic Surgery: *Oral and Written.* Milwaukee, May 1960. Final date for filing application was January 1. Corresponding Secretary, Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

American Board of Proctology: *Oral and Written, Parts I and III,* Philadelphia, Sept. 24. Final date for filing application is June 30. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

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Board of Thoracic Surgery: *Oral.* May 1960. Final date for filing application was Dec. 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

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War II; for many years surgeon for the U. S. Steel Corporation; member of the staff of St. Francis General Hospital, where he died Jan. 1, aged 57, of acute myocardial infarction.

Byers, Earle John Ⓜ Grand Rapids, Mich.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; died in the Blodgett Memorial Hospital Dec. 23, aged 74.

Claiborn, Drura R. Ⓜ Bigtimber, Mont.; Missouri Medical College, St. Louis, 1898; veteran of World War I; served as mayor, and on the Sweet Grass County High School board; died in the Sweet Grass Community Hospital Dec. 30, aged 84, of coronary occlusion.

Corbell, Robert Lawrence Jr., Portsmouth, Va.; Medical College of Virginia, Richmond, 1941; interned at the Norwalk (Conn.) General Hospital; veteran of World War II; died Jan. 3, aged 46.

Davis, Richard Sharpless Ⓜ Philadelphia; Medico-Chirurgical College of Philadelphia, 1906; died in the Germantown Hospital Dec. 24, aged 76, of bronchopneumonia.

Desrochers, Bernard Charles Ⓜ Adams, Mass.; Tufts College Medical School, Boston, 1924; member of the Industrial Medical Association; veteran of World War II; member of the staff of the W. B. Plunkett Memorial Hospital; vice-president of the South Adams Savings Bank; died Jan. 14, aged 60.

Dill, Lawrence Love, Logansport, Ind.; University of Michigan Homeopathic Medical School, Ann Arbor, 1910; died in St. Joseph's Hospital Jan. 2, aged 75.

Felix, Frank Carl, Rocky River, Ohio; University of Wooster Medical Department, Cleveland, 1893; died Dec. 23, aged 92.

Gann, Dewell Jr. Ⓜ Benton, Ark.; Indiana University School of Medicine, Indianapolis, 1913; fellow of the International College of Surgeons and the American College of Surgeons; served on the faculty of the University of Arkansas School of Medicine in Little Rock, where he was affiliated with St. Vincent's Infirmary, Little Rock Hospital, and the Arkansas Baptist Hospital; veteran of World War I; died Jan. 2, aged 69.

Gibson, Milton Reynolds Ⓜ Raleigh, N. C.; University of Maryland School of Medicine, Baltimore, 1905; past-president of the Wake County Medical Society, Raleigh Academy of Medicine, and the North Carolina Eye, Ear, Nose and Throat Society, of which he was formerly secretary; for many years associated with the Rex Hospital; died Jan. 11, aged 77.

Gillette, Tracy James, Owego, N. Y.; Albany (N. Y.) Medical College, 1942; served an internship at the U. S. Marine Hospital in Staten Island and the U. S. Marine Hospital in Norfolk, Va.; served a residency at the Binghamton (N. Y.) City Hospital; veteran of World War II; died Nov. 4, aged 47, of cancer.

Goodwin, Perry Bird Ⓜ Peoria, Ill.; College of Physicians and Surgeons, Baltimore, 1890; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; formerly on the staff of the St. Francis Hospital; for many years associated with the Proctor Hospital, where he died Jan. 1, aged 81.

Gramley, William Ⓜ Detroit; University of Michigan Homeopathic Medical School, Ann Arbor, 1913; veteran of World War I; served on the staffs of the Grace, East Side General, and St. John's hospitals; died Dec. 31, aged 72, of acute myocardial infarction.

Greenberg, Max Ⓜ Linden, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1924; fellow of the American College of Cardiology; veteran of World War I; a founder and board member of the Linden Public Library; died Jan. 11, aged 66.

Gullion, Omar Ray Ⓜ San Jose, Calif.; Rush Medical College, Chicago, 1907; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; past-president of the Lane County (Ore.) Medical Society; for many years practiced in Eugene, Ore.; died in Santa Monica Dec. 30, aged 81.

Hall, James A. J. Ⓜ Detroit; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1910; associated with the Grace Hospital, where he died Jan. 15, aged 78.

Hamilton, Hugh Gerard Ⓜ Kansas City, Mo.; born in Kansas City March 27, 1905; University of Pennsylvania School of Medicine, Philadelphia, 1931; specialist certified by the American Board of Obstetrics and Gynecology; certified by the National Board of Medical Examiners; founding fellow of the American College of Obstetricians and Gynecologists; member of the Central Association of Obstetricians and Gynecologists; fellow of the American College of Surgeons; veteran of World War II; associated with St. Mary's, St. Joseph, and Kansas City General hospitals; died in a hospital at Pachuca, Mexico, Jan. 4, aged 54.

Harper, Thomas Bailey Ⓜ St. Stephen, S. C.; Medical College of South Carolina, Charleston, 1920; for many years vice-chairman of the South Carolina Penitentiary System Board; served as president of St. Stephen Lions Club; died in Charleston Jan. 6, aged 64.

Henner, Robert Ⓜ Chicago; University of Illinois College of Medicine, Chicago, 1934; specialist certified by the American Board of Otolaryngology;

member of the American Academy of Ophthalmology and Otolaryngology and the American Laryngological, Rhinological and Otological Society; on the faculty of his alma mater; associated with the Highland Park (Ill.) Hospital and the Michael Reese Hospital, where he served an internship, and where he died Jan. 21, aged 50.

Inman, Thomas George Ⓜ San Francisco; Cooper Medical College, San Francisco, 1894; also a graduate in pharmacy; emeritus clinical professor of medicine at Stanford University School of Medicine, where he joined the faculty in 1915; formerly associated with the U. S. Public Health Service; died Jan. 10, aged 87.

Jablonsky, Jacob G., Brooklyn; Universität Bern Medizinische Fakultät, Switzerland, 1936; veteran of World War II; died Oct. 15, aged 50, of acute coronary thrombosis.

Johnson, John Martin Jr. Ⓜ Big Stone Gap, Va.; University of Virginia School of Medicine, Charlottesville, 1948; served a residency at the Henry Ford Hospital in Detroit; from July, 1951, to July, 1953, an officer in the medical corps of the U. S. Army Reserve; killed Dec. 28, aged 37, when his car skidded on a wet highway and plunged into the Pound River.

Jones, Howard Hiram, Salamonia, Ind.; Indiana University School of Medicine, Indianapolis, 1915; county coroner for four years; served overseas during World War I; died in the Union City (Ind.) Memorial Hospital Jan. 1, aged 74.

Jutte, Max Ernest Ⓜ New York City; University and Bellevue Hospital Medical College, New York City, 1906; died in the Meadowbrook Hospital in Hempstead, N. Y., Jan. 14, aged 84.

Kellogg, James Henry Ⓜ Bemus Point, N. Y.; University of Buffalo School of Medicine, 1902; past-president of the board of education; served on the staffs of the Woman's Christian Association Hospital and the Jamestown General Hospital in Jamestown; died in St. Petersburg, Fla., Jan. 2, aged 83.

Lackey, Sylvester Jacob Ⓜ Clarion, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1908; member of the American Academy of General Practice; died in Pleasantville Dec. 28, aged 76, of generalized arteriosclerosis.

Lalor, Joseph Clinton Ⓜ Oregon, Wis.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1908; died in Madison Dec. 23, aged 77.

Lattimore, J. A. C., Louisville, Ky.; Meharry Medical College, Nashville, Tenn., 1901; past-president of the National Medical Association; died Dec. 31, aged 85.

Leeming, Frank Charles Ⓜ Chicago; born in Chicago, Dec. 18, 1892; University of Louisville (Ky.) School of Medicine, 1921; specialist certified by the American Board of Pediatrics; formerly on the faculty of Loyola University School of Medicine; associated with the Little Company of Mary Hospital in Evergreen Park, Ill., City of Chicago Municipal Tuberculosis Sanitarium, where he was staff president, La Rabida Jackson Park Sanitarium, and the Mercy Hospital; for many years on the staff of the Chicago Wesley Memorial Hospital, where he died of coronary occlusion Jan. 10, aged 66.

Lichtenstein, George, New York City; Columbia University College of Physicians and Surgeons, New York City, 1907; died Dec. 20, aged 80.

Lines, Ezra Austin, San Antonio, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1897; formerly associated with the Indian Service; died in December, aged 83.

Livingston, Everett Alexander Ⓜ Gibson, N. C.; University of Maryland School of Medicine, Baltimore, 1912; past-president of the Scotland County Medical Society; died of uremia in the Scotland County Memorial Hospital, Laurinburg, Dec. 24, aged 70.

Lynch, James Madison, Fairview, N. C.; University of Maryland School of Medicine, Baltimore, 1904; past-president of the Buncombe County Medical Society; for many years practiced in Asheville, where he was associated with the Biltmore Hospital; died in the Memorial Mission Hospital of Western North Carolina, Asheville, Nov. 22, aged 82, of mesenteric thrombosis.

MacDougall, Edward Lewis Ⓜ Warren, Ohio; Western Reserve University School of Medicine, Cleveland, 1935; interned at the Youngstown Hospital in Youngstown, Ohio; veteran of World War II; on the staff of the Trumbull Memorial Hospital, where he died of hemorrhage of throat Dec. 26, aged 51.

McCord, Bert, Gadsden, Ala.; Northwestern University Medical School, Chicago, 1929; died Jan. 5, aged 55.

McGill, Chester Francis, Portsmouth, N. H.; Tufts College Medical School, Boston, 1915; veteran of World War I; served in the regular Navy; formerly on the staff of the Laconia (N. H.) State Hospital; died in the Franklin (N. H.) Hospital Dec. 22, aged 71.

McIntosh, Ronald Buchanan Ⓜ Selinsgrove, Pa.; Boston University School of Medicine, 1926; member of the American Psychiatric Association; served as clinical director of Norristown (Pa.) State Hospital; died of thromboangitis obliterans in Sunbury Dec. 5, aged 61.

Macon, William Linus, Hickory Point, Tenn.; Vanderbilt University School of Medicine, Nashville, 1901; died of bilateral pneumonia in the Memorial Hospital, Clarksville, Dec. 13, aged 81.

Magidson, Joshua Ⓜ Chicago; Chicago Medical School, 1951; interned at the Grace Hospital in Detroit; served a residency at the Veterans Administration Hospital in Hines; died Dec. 23, aged 38.

Mantz, Francis Alphonso Ⓜ Bala-Cynwyd, Pa.; Medico-Chirurgical College of Philadelphia, 1904; for many years practiced in Philadelphia, where he was on the faculty of the University of Pennsylvania School of Medicine; died in the Neurological Hospital in Kansas City, Mo., Jan. 6, aged 82.

Marcus, Joseph Harvey, Los Angeles; Jefferson Medical College of Philadelphia, 1914; member of the American Academy of Pediatrics; died in the Cedars of Lebanon Hospital Dec. 24, aged 68.

Marshall, William Riddle Ⓜ Clinton, Ill.; Chicago College of Medicine and Surgery, 1909; served as president and secretary-treasurer of the DeWitt County Medical Society; on the staff of the John Warner Hospital; died of myocarditis Dec. 11, aged 84.

Martin, Harry Givhan Ⓜ Albertville, Ala.; Tulane University School of Medicine, New Orleans, 1948; interned at the Jefferson-Hillman Hospital in Birmingham, where he served a residency; served in the medical corps of the U. S. Naval Reserve; co-owner of the Sand Mountain Infirmary; died Jan. 6, aged 35, in an automobile accident.

Martin, Moir Saunders Ⓜ Mount Airy, N. C.; University College of Medicine, Richmond, 1905; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; past-president of the Surry-Yadkin Counties Medical Society; served as chairman of the school board of Mount Airy; a director of the First National Bank; one of the founders and chairman of the board of trustees of the Northern Hospital of Surry County, where he died Jan. 4, aged 76.

Maurer, Siegfried Ⓜ Tigerton, Wis.; Rush Medical College, Chicago, 1923; died Dec. 13, aged 69.

Mayes, Walter Charley, Newport Beach, Calif.; University of Texas School of Medicine, Galveston, 1905; at one time a medical missionary in Korea; served as secretary of the Orange County Medical Society; died in the Hoag Memorial Hospital-Presbyterian Dec. 31, aged 77.

Meranze, Theodore Ⓜ Philadelphia; Jefferson Medical College of Philadelphia, 1932; served an internship and residency at the Mount Sinai Hospital; specialist certified by the American Board of Radiology; member of the American College of Radiology; associated with Albert Einstein Center, southern division, and Doctors Hospital; died Dec. 30, aged 54.

Messina, Salvatore Joseph Ⓜ Boston; born in Brooklyn Jan. 1, 1911; Boston University School of Medicine, 1937; interned at St. Vincent Hospital in Worcester, Mass.; specialist certified by the American Board of Dermatology; member of the American Academy of Dermatology and Syphilology; certified by the National Board of Medical Examiners; veteran of World War II; on the faculty of his alma mater; associated with the Glover Memorial Hospital, Needham, Mass., Massachusetts Memorial Hospitals, Boston City Hospital, and St. Elizabeth's Hospital; died of acute myocardial infarction in the Newton-Wellesley Hospital in Newton Dec. 30, aged 48.

Mohney, Ford Curtis Ⓜ Mount Lebanon, Pa.; Jefferson Medical College of Philadelphia, 1921; associated with the Allegheny General Hospital in Pittsburgh; died Jan. 6, aged 62.

Montelepre, Philip Ⓜ New Orleans; St. Louis University School of Medicine, 1924; for many years assistant coroner of Orleans Parish; served as an examining physician for the Metropolitan Life Insurance Company and medical examiner for the state athletic commission; medical director and founder of the Montelepre Memorial Hospital, where he died Dec. 14, aged 62.

Morehead, Carl Edgar Ⓜ Parkersburg, W. Va.; University of Louisville School of Medicine, Louisville, Ky., 1934; also a graduate in pharmacy; interned at the Louisville City Hospital; served as health officer of Wood County; on the staff of the Camden-Clark Memorial Hospital; died Jan. 6, aged 53, of coronary thrombosis.

Mosely, John Miller, Arcadia, La.; Memphis (Tenn.) Hospital Medical College, 1903; formerly vice-president of the state board of health; served as a member of the Bienville Parish School Board; at one time superintendent of the old Charity Hospital in Shreveport; died Dec. 6, aged 79.

Murphy, John Michael, Florence, Mass.; Tufts College Medical School, Boston, 1919; associate medical examiner in Hampshire County; veteran of World War I; formerly member and chairman of the Northampton Board of Health and served as city physician and school physician, retiring from the latter post in September, 1958; a staff member of the Cooley Dickinson Hospital in Northampton; died Dec. 31, aged 67.

Myers, Jack Wendell Ⓜ El Reno, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1943; interned at the Wesley Hospital in Oklahoma City; served a residency at the City and County Hospital in Fort Worth, Texas; veteran of World

War II; served in the medical corps of the U. S. Air Force Reserve during the Korean War; president of the Canadian County Cancer Society; on the staff of the Parkview Hospital; died Jan. 3, aged 42.

Myers, William Throphilus, Aldrich, Mo.; Barnes Medical College, St. Louis, 1901; also a druggist; died Jan. 3, aged 83.

Nisley, Glen Ⓜ Chillicothe, Ohio; Ohio State University College of Medicine, Columbus, 1915; veteran of World War I; died Jan. 2, aged 72.

Northway-Meyer, Oscar Ⓜ Seattle; New York Homeopathic Medical College and Flower Hospital, New York City, 1895; past-president of the Orange County (N. Y.) Medical Association; served as mayor of Monticello, N. Y., and was president of the board of education of Middletown, N. Y., where he was associated with the Horton Memorial Hospital; died Dec. 12, aged 88.

Oberwager, John Ⓜ New York City; Columbia University College of Physicians and Surgeons, New York City, 1906; served as director of the bureau of health education and director of the sanitary bureau; at one time general medical officer of the department of health; died of acute myocardial infarction in the Mount Sinai Hospital Jan. 2, aged 75.

Olson, Donald Lawrence Ⓜ Fargo, N. D.; born in Minneapolis March 7, 1920; University of Minnesota Medical School, Minneapolis, 1951; interned at the Minneapolis General Hospital in Minneapolis, where he served a residency; served a residency at the Veterans Administration Hospital in Minneapolis, University of Minnesota Hospitals in Minneapolis, Gillette State Hospital for Crippled Children in St. Paul, and the Shriners Hospital for Crippled Children in Minneapolis; veteran of World War II; on the staff of St. John's Hospital; consultant at the Veterans Administration Center; died of mediastinal hemorrhage in St. Ansgar's Hospital, Moorhead, Dec. 13, aged 39.

O'Rourke, Donald Hunter Ⓜ Denver; Rush Medical College, Chicago, 1917; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology and the Association for Research in Ophthalmology; veteran of World War I; served in the regular Navy; formerly president and vice-president of the Pacific Coast Oto-Ophthalmological Society; on the staffs of the Children's, Denver General, and Mercy hospitals; died of coronary occlusion Dec. 27, aged 66.

Peabody, Charles H. Ⓜ Youngstown, Ohio; Toledo Medical College, 1898; died of cerebral arteriosclerosis Dec. 24, aged 83.

Pennington, George E., Broken Bow, Neb.; Ensworth Medical College, St. Joseph, Mo., 1902; died Jan. 6, aged 84.

Perrin, David Amos Ⓜ Chillicothe, Ohio; Starling Medical College, Columbus, 1900; past-president of the Ross County Medical Society; served during World War I; died in the Chillicothe Hospital Jan. 1, aged 85.

Peterson, Paul Andrew Jr. Ⓜ Fargo, N. D.; University of Minnesota Medical School, Minneapolis, 1951; interned at the Ancker Hospital in St. Paul, where he served a residency; served a residency at the Bismarck (N. D.) Hospital; formerly a fellow in surgery at the Mayo Foundation, Rochester, Minn.; died of renal failure in Rochester, Minn., Dec. 26, aged 34.

Philpot, Van Buren Ⓜ Memphis, Tenn.; Memphis (Tenn.) Hospital Medical College, 1912; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; past-president of the Mississippi State Hospital Association; for many years superintendent of the North Mississippi Hospital in Holly Springs and superintendent and surgeon in charge of the Houston (Miss.) Hospital; founder and formerly editor of the *Mississippi Doctor*; died in the Baptist Memorial Hospital Dec. 14, aged 71.

Piazza, Leonard Frank Ⓜ Michigan City, Ind.; Indiana University School of Medicine, Indianapolis, 1933; member of the American Academy of General Practice; vice-president of St. Anthony Hospital; died of skull fracture near Gary Dec. 17, aged 55.

Pick, Ernst Peter, New York City; Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, 1896; for many years on the faculty of Columbia University College of Physicians and Surgeons as clinical professor of experimental pharmacology; a member of many scientific and honorary societies including the Society for Experimental Biology and Medicine, American Association for the Advancement of Science, American College of Cardiology, the Harvey Society, and the New York Academy of Medicine; associated with the Mount Sinai Hospital, where he died Jan. 15, aged 87.

Pinkerton, Benjamin Gershon, Los Angeles; Washington University School of Medicine, St. Louis, 1900; on the staff of the Methodist Hospital; died of cerebral thrombosis in the Hollywood Presbyterian Hospital Dec. 17, aged 81.

Pitkin, Edith Winifred, Congers, N. Y.; Tufts College Medical School, Boston, 1906; on the staff of the Nyack (N. Y.) Hospital, where she died Jan. 3, aged 82.

Podos, Louis Reuben, Charleston, S. C.; New York Homeopathic Medical College and Flower Hospital, New York City, 1914; died in Atlanta, Ga., Dec. 22, aged 74, of hypertensive heart disease.

Posey, William Campbell Jr. Ⓜ Bryn Mawr, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1939; interned at the Bryn Mawr Hospital, where he was on the staff; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the International College of Surgeons; associated with the Graduate Hospital of the University of Pennsylvania in Philadelphia; died Jan. 2, aged 45.

Potekin, Jesse Sanford Ⓜ Woodland Hills, Calif.; University of Minnesota Medical School, Minneapolis, 1931; veteran of World War II; died Jan. 8, aged 54.

Prentiss, Harley Merton Ⓜ Nowata, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1918; past-secretary of the Washington Nowata County Medical Society; died of pulmonary edema in Rochester, Minn., Dec. 26, aged 67.

Preston, Paul James Ⓜ Minneapolis; Rush Medical College, Chicago, 1915; served on the staff of the Asbury Methodist Hospital; died Dec. 29, aged 70.

Preston, William Bowker, Logan, Utah; University of Illinois College of Medicine, Chicago, 1916; veteran of World War I; for many years physician at the Utah University; died Jan. 5, aged 73.

Proff, Harold Philip Ⓜ Olympia, Wash.; University of Minnesota Medical School, Minneapolis, 1941; interned at the Hurley Hospital in Flint, Mich.; member of the American Academy of General Practice; veteran of World War II; on the staff of St. Peter Hospital; died Jan. 3, aged 45.

Pugh, John Ⓜ Cotton Valley, La.; Memphis (Tenn.) Hospital Medical College, 1905; member of the American Academy of General Practice; died Dec. 30, aged 89.

Puglisi, Anthony Salvatore, Brooklyn; Boston University School of Medicine, 1926; on the staff of the Lutheran Medical Center; died Oct. 25, aged 58.

Pyle, William Thomas Ⓜ Pittsburgh; Ohio Medical University, Columbus, 1897; veteran of World War I; died in Venice, Fla., Dec. 14, aged 92.

Reddick, Walter Grady Ⓜ Dallas, Texas; born in Dallas Jan. 24, 1899; Northwestern University Medical School, Chicago, 1925; interned at the Cook County Hospital in Chicago; clinical professor of internal medicine, University of Texas Southwestern Medical School; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the American Diabetes Association, Dallas Southern Clinical Society, Alpha Omega Alpha, Phi Beta Pi, Phi Beta Kappa, and Alpha Tau Omega; veteran of World War II; in 1945 received the award of merit from the alumni association of his alma mater; served as physician-in-chief of Parkland Memorial Hospital and attending physician at Baylor University Hospital; died Dec. 31, aged 60.

Richardson, Arthur Lee Ⓜ Arcadia, Calif.; University of Michigan Medical School, Ann Arbor, 1932; interned at the Providence Hospital in Detroit; for many years associated with the city health department in Pasadena; on the staffs of the Alta Vista and Collis P. and Howard Huntington Memorial hospitals, in Pasadena; died Jan. 4, aged 57.

Roberts, Bryan Nazer Ⓜ Hillsboro, N. C.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1925; died Jan. 1, aged 61.

Rosedale, Charles, Rockport, Mass.; College of Physicians and Surgeons, Boston, 1901; died Dec. 9, aged 92.

Rosen, Charles Edward Ⓜ Englewood Cliffs, N. J.; New York Medical College, Flower and Fifth Avenue Hospitals, New York City, 1939; interned at the Christ Hospital in Jersey City; certified by the National Board of Medical Examiners; served as president of the Hudson County Medical Society; veteran of World War II; formerly practiced in Union City, where he was school physician and member of the board of education; on the staff of the Christ Hospital, Jersey City, where he died Jan. 19, aged 46.

Rundstrom, Karl Gustav Ⓜ Hollywood, Fla.; Chicago Medical School, 1933; served on the staffs of the Walther Memorial and Bethany hospitals in Chicago; died Jan. 5, aged 56.

Russell, Lecky Harper, Elmhurst, N. Y.; Ohio State University College of Medicine, Columbus, 1916; died in the Horace Harding Hospital Oct. 11, aged 70, of cerebral hemorrhage.

Saltzman, Nathan Leon, Cincinnati; University of Cincinnati College of Medicine, 1912; associated with the Cincinnati General Hospital and the Jewish Hospital, where he died Dec. 9, aged 74.

Schlesinger, Henry Ⓜ Pittsburgh; Baltimore Medical College, 1913; specialist certified by the American Board of Otolaryngology; fellow of the American College of Surgeons; served on the staff of the Columbia Hospital in Wilkinsburg, Pa.; died Jan. 12, aged 77.

Seaver, Edwin Pliny Jr. Ⓜ New Bedford, Mass.; born in Waban, Sept. 24, 1880; Harvard Medical School, Boston, 1905; specialist certified by the American Board of Otolaryngology; member of the American Laryngological, Rhinological and Otological Society; fellow of the American College of Surgeons; past-president of the Massachusetts Medical Society, South Bristol and New Bedford districts, and the New Bedford Harvard Club; in 1956 received the Victor Stoll Memorial Award from the Group for Research in Oral Orthopedics for his contribution in the field of oral orthopedics; served on the staff of St. Luke's Hospital, where he died Jan. 16, aged 79.

Seidenstein, Harold Ⓜ New York City; New York University College of Medicine, 1937; specialist certified by the American Board of Orthopedic Surgery; member of the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; veteran of World War II; associated with the Hospital for Joint Diseases and the Lebanon Hospital; died Jan. 10, aged 45.

Seltzer, Sol Norris Ⓜ Redlands, Calif.; Detroit College of Medicine and Surgery, 1937; interned at St. Francis Hospital in Peoria, Ill.; served a residency at the Woman's Hospital in Detroit and the City of Hope Medical Center in Duarte; died Dec. 29, aged 49.

Shulman, David Nathaniel, New Haven, Conn.; Johns Hopkins University School of Medicine, Baltimore, 1917; associate clinical professor of medicine at Yale University School of Medicine; veteran of World War II; associated with the Grace-New Haven Community Hospital; died in the Veterans Administration Hospital in West Haven Dec. 30, aged 67.

Siemsen, Walter Johannes Ⓜ Kalamazoo, Mich.; State University of Iowa College of Medicine, Iowa City, 1926; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; interned at the Butterworth Hospital in Grand Rapids; at one time a fellow in pediatrics at the Mayo Foundation in Rochester, Minn.; served a residency at the Bobs Roberts Memorial Hospital for Children in Chicago; veteran of World War II; died in the Bronson Hospital Dec. 6, aged 58.

Sims, John Lester Ⓜ Joplin, Mo.; St. Louis University School of Medicine, 1909; past-president of the Jasper County Medical Society; past-president of the staffs of Freeman and St. John's hospitals; died Dec. 23, aged 76.

Smith, Irene Sutter, La Crosse, Wis.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1911; died Nov. 24, aged 70.

Snyder, George Henry Ⓜ Columbus, Ohio; Starling-Ohio Medical College, Columbus, 1911; veteran of World War I; died Dec. 12, aged 75.

Sparling, Harry Perkins, London, Ohio; Starling-Ohio Medical College, Columbus, 1910; died Dec. 9, aged 76.

Stork, Edwin Gordon, Philadelphia; Jefferson Medical College of Philadelphia, 1914; died Sept. 27, aged 71.

Thorek, Max Ⓜ Chicago; born in Hungary March 10, 1880; Rush Medical College, Chicago, 1904; founder and secretary general of the International College of Surgeons, and editor of its journal; a founder of the American Hospital, Chicago, where he was chief surgeon; past-president and secretary, American Physicians' Art Association; professor of surgery, Cook County Graduate School of Medicine; at one time taught at Loyola University School of Medicine, Chicago; member of the American College of Gastroenterology, Phi Lambda Kappa, American Society of Plastic and Reconstructive Surgery, Royal Society of Arts, and the Royal Photographic Society of Great Britain; honorary fellow, Philippine College of Surgeons, Royal Academy of Surgery, Italy, Surgical Society of Rome; honorary member, Golden Key Society of the University of Vienna, Chiba Medical Association, Japan, Japan Surgical Association, Royal Surgical Society, Sofia, Bulgaria, and the Gastroenterology Society, Brussels; corresponding member, Society of Science and Medicine, Lisbon, Surgical Society of Portugal, Surgical Academy, Mexico; corresponding fellow, Peruvian Surgical Society and the Venezuelian Society of Surgery; honorary corresponding member, Egyptian Medical Association; fellow, Eugenics Society, American Medical Writers' Association, Brazilian College of Surgeons, National Academy of Medicine, Colombia Medical Society, Parana, Brazil, International Hospital Association, International Society of Gastroenterology, International College of Anesthetists, and International Anesthetic Research Society; honors include the Knight Crown of Italy, Order of Merit of Italy, 1927, chevalier, Legion d'honneur, France, 1937, "Order of the Sun," Peru, Order of the Aztec Eagle, Mexico, and Gold Medal of Honor, Venezuela, 1941; received the Distinguished Citizen Medal from the Veterans of Foreign Wars; a grand officer, Order of Merit, Argentina; in 1937, U. S. Delegate to the International Congress of Hepatic Insufficiency in France; Cushing Lecturer at McGill University, Montreal, in 1954; gave the Collier-Ford-Martin Oration of the Pennsylvania Proctologic Society in 1958; consulting editor, *Arquivos de Cirugia Clínica e Experimental;* general adviser to the American Physicians Literary Guild; consulting surgeon to the Municipal Tuberculosis Sanitarium and attending surgeon, Cook County Hospital; at one time on the staff of the West Side Dispensary; received the honorary degree of doctor of science from Iowa Wesleyan College, Mount Pleasant, Iowa; author of "A Surgeon's World" and contributor to many professional journals; won more than 2,000 prizes as a photographer; died of pulmonary infarction Jan. 25, aged 79.

FOREIGN LETTERS

FINLAND

Treatment of Toxic Nodular Goiter with I^{131}.—B.-A. Lamberg and co-workers (*Acta med. scandinav.* 165:245-258, 1959) treated a series of 144 patients who had hyperthyroidism with radioactive iodine (I^{131}). In 12 of these patients the thyroid was not demonstrable, 34 had a diffuse goiter, and 98 had a nodular goiter. Remissions of symptoms occurred in 71.8% of the first two groups, and 21.7% became hypothyroid. In the group with nodular goiter, the corresponding figures were 81.6 and 8.2%. In nine patients (6.3%) the response was characterized as failing. Two of these patients died, and the others were operated on or given antithyroid drugs. In seven patients (4.9%) a severe post-treatment reaction occurred. In two patients the condition was classified as thyroid storm and in three as impending storm; in one patient a myocardial infarction occurred. In 11.1% a temporary aggravation of the thyrotoxicosis occurred. Temporary hypothyroidism was diagnosed in 7.7%. There was a postoperative relapse in 31 patients. Of these, 87.1% became euthyroid. In 27 patients there was a recurrence after long-term antithyroid treatment. Of these patients 74.1% became euthyroid. In three patients there was a marked increase of the thyrohypophysial eye syndrome and in many there was an increase of the ocular signs. In one patient, however, there was a gradual improvement of the ocular condition.

The present results substantiated the fact that the occurrence of hypothyroidism after treatment with I^{131} was definitely less in patients with toxic nodular goiter than in those with diffuse goiter. With increasing experience, the incidence might even be brought to a lower level. It seemed, however, that the dose was not the only factor influencing the production of hypothyroidism. Another factor was the sensitivity of the cells to radiation. After observing that some fairly serious reactions occurred after administration of I^{131} the authors stated that the regions in Northern Europe in which goiter is endemic probably exhibited special problems because of the presence of multinodular goiter. It seemed possible that the careful use of antithyroid therapy before and after giving I^{131} might greatly diminish the occurrence of such reactions.

The risk of producing thyroid carcinoma by giving antithyroid agents with I^{131} seemed to be slight. The number of patients needing such a combined treatment was small, and they belonged to an age group where such risks could be taken. In presenting a general scheme for the different types of treatment related to nature of goiter and age, the authors stated that after the age 40 to 45 years an increasing number of patients will be treated with I^{131}, including those with a large nodular goiter, the greatest advantage with this type of treatment in an endemic goiter zone being the curative effect in patients with pronounced intrathoracic nodular goiter and hyperthyroidism. In Finland goiter is almost always multinodular in patients over 60 years of age, an age group in which the proportion of patients in whom surgery is to be avoided is fairly large.

FRANCE

Test for Arteritis Obliterans.—At a meeting of the Société française de Cardiologie in May, Lian and Tursz reported on the reabsorption time of wheals produced by the intradermal injection of two drops of a 9:1,000 sodium chloride solution in patients with arteritis of the extremities. In patients with arteritis the sodium chloride solution is injected in the thigh, knee, leg, instep, and big toe. The reabsorption time, which in normal subjects is longer than 30 minutes, is reduced to less than 20 minutes and often to about 4 minutes in patients with arteritis obliterans. If the obliteration is in the middle or the lower section of the femoral artery, the reabsorption time is normal at the thigh. If the obliteration is higher the reabsorption at the thigh is accelerated.

The authors applied the test before and after exercise. In some subjects effort accelerated reabsorption. The reabsorption time is meaningless if the patient suffers from renal, cardiac, or hepatic insufficiency, but it is not influenced by the presence of varices. The test is equally applicable to the study of vascular conditions in the upper extremities. If the obliteration involves the subclavian artery, the reabsorption is accelerated in the forearm. The variation from the normal time, however, is less marked in the upper than in the lower extremities.

Chronic Progressive Polyarthritis.—At the Sixth International Congress of Therapeutics in Strasbourg in October, M. H. Picard reported that he and his co-workers treated a series of 70 patients who had chronic progressive polyarthritis with a combination

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The items in these letters are contributed by regular correspondents in the various foreign countries.

of copper and silver gluconate and colloidal gold, all active ion exchangers. The author added fluorine, which is effective in the treatment of osteoporosis and capsuloligamental disturbances. He also gave potassium gluconate intramuscularly to increase the anti-inflammatory activity of the catalyzers.

The patients were divided in groups according to the stage of their disease. In 24 patients in stage 1, in whom the duration of polyarthritis was one to four years, with acute inflammation, moderate ankylosis, and a sedimentation rate of more than 25 mm., there was satisfactory improvement after a period of 6 to 24 months of treatment. This improvement was maintained for two years. In 18 of these patients the sedimentation rate and the serum globulin levels returned to normal. In the rest the sedimentation rate was brought to between 15 and 20 mm. In 32 patients in stage 2, with polyarthritis of four to five years' duration and with evident articular alterations but incomplete ankylosis, the painful inflammatory manifestation decreased but the articular deformations persisted. The therapy was ineffective in 14 patients in stage 3, who had had polyarthritis for more than 15 years.

Dexamethasone for Rheumatic Disease.—At the same meeting Rubens-Duval and co-workers reported that they treated a series of 10 patients, 9 of whom had chronic progressive polyarthritis and 1 of whom had ankylosing spondylarthritis, with dexamethasone. With one exception, these patients had already been treated with deltacortisone and deltahydrocortisone. The authors first gave dexamethasone in doses that produced results similar to those of deltacortisone. Then the dosage was increased in order to obtain better results. The largest dose given was 8 to 10 mg. The dosage was then gradually decreased until it reached the lowest amount required for maintenance of the improvement obtained. The maintenance dosage was established at 2 to 3 mg. a day. As a therapeutic adjuvant the authors used androgens.

The results were excellent in all patients. Not only did the pain decrease while the patients were resting but also some patients regained mobility of which they had been deprived for a long time. The sedimentation rate decreased in eight of the patients. These results were definitely better than those obtained with deltacortisone. With identical doses the therapeutic power of dexamethasone was five to six times greater than that of deltacortisone. One of the polyarthritic patients who required a large dose because of an articular lesion died of pneumonia in spite of treatment with antibiotics. At autopsy a recent prepyloric ulcer in the process of perforating into the peritoneal cavity was found. Three patients had temporary edematous manifestations, and in two hypertensives the blood pressure increased. Most patients complained of sleep disorders, swelling of the face, and excessive sweating. Five patients observed the development of cutaneous ecchymoses and even purpura after light trauma. The authors used the same treatment in two patients with sciatica, one with lumbago, and one with scapulohumeral arthritis. They too were definitely relieved, and at the end of the treatment their recovery was complete.

INDIA

Potassium Deficiency and Operation.—Srivastava and Khanna studied a series of 50 patients before and after various operations (*J. Indian M. A.*, vol. 33, Dec. 16, 1959). The potassium, sodium, and chloride content of the blood were determined on admission, on the morning of operation, and at frequent intervals during the postoperative period till the potassium values returned to normal. None of the patients had a deficient preoperative serum potassium level. Most of them ate a normal diet until the night before operation. The postoperative urinary excretion of potassium was estimated in some patients and was found to be the same or even in excess of the preoperative level, although there was no intake of potassium during this period. In most patients the total output of urine was decreased, but the fall in excretion of potassium was not proportional to it.

Most patients did not receive any potassium for 24 hours after operation and some for up to four days. These latter had continuous gastrointestinal suction and fluid given intravenously after such operations as partial gastrectomy and hemicolectomy. In some of these, although the total potassium excretion was reduced, an adequate amount was still excreted in spite of the absence of potassium intake and loss of potassium through gastrointestinal suction. The serum potassium level in some patients showed a slight postoperative rise but then fell to a degree which varied from patient to patient. The extent of the fall was proportional to the severity of the operation. After herniorrhaphy and appendectomy the fall was less than that after partial gastrectomy, hemicolectomy, or thoracoplasty. Patients receiving fluid intravenously for a long time showed a constant fall in the serum potassium level. This fall was more marked when associated with gastrointestinal suction. Administration of 5 or 10% dextrose solution increased the total urinary excretion of potassium and was accompanied by diuresis after 5% dextrose solution. Only two patients showed severe hypochloremia, and they had pyloric stenosis and did not respond to 5% dextrose in saline solution given intravenously. They remained drowsy, listless, and weak. Recovery occurred after normal diet was instituted supplemented in one patient with potassium salt.

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ACTH-Treatment of Acute Viral Hepatitis.—O. Naglo and co-workers (*Acta med. scandinav.* 165:167-171, 1959) treated 50 patients who had acute uncomplicated viral hepatitis with ACTH. No differentiation was made between patients with infectious hepatitis and those with inoculation hepatitis. Only patients aged between 15 and 60 years and who had a serum bilirubin value of 3.0 mg. or more per 100 ml. were included. The series was divided into an ACTH-treated and a control group, each group consisting of 25 patients. The mean age of the ACTH-treated group was 36.0 and of the controls 28.6 years. All patients who received ACTH showed decreasing serum bilirubin levels, while among the controls an increase occurred in three patients. The mean of the serum bilirubin level decreased more rapidly in the treated group than in the controls, but no significant difference could be demonstrated. The thymol turbidity also showed a more rapid decrease in the treated group. This difference was significant. A bilirubin level of 2 mg. per 100 ml. or less was reached within a shorter period in the treated than in the control group, as was a sulfobromophthalein level of 10% or less in the sulfobromophthalein retention test.

The difference was, however, not significant. The advantages of the ACTH treatment, however, seemed to be counteracted by the risk of side-effects. Furthermore patients with acute viral hepatitis, with few exceptions, were completely restored to health by the usual methods of treatment. Therefore routine ACTH or cortisone treatment did not seem to be justified. The question as to the effect of these hormones in connection with fulminating or in otherwise complicated cases of acute hepatitis or as to their ability to prevent chronic hepatitis or cirrhosis was perhaps of greater practical importance. It had been emphasized that the adrenals in infectious conditions and particularly in liver affections were subject to deficient function. Consequently, the authors concluded that direct substitutional therapy with cortisone seemed to be preferable to treatment with ACTH.

UNITED KINGDOM

Alcohol and Driving.—A Medical Research Council memorandum described experiments designed to determine the effect of small doses of alcohol on a skill resembling the driving of an automobile (Medical Research Council Memorandum 38, Her Majesty's Stationery Office, 1959). Investigations were also made on individual variations in response to alcohol, particularly in relation to personality differences, and on the comparison of methods of estimating blood alcohol by Professor Drew. The subjects were automobile drivers of high intelligence and were moderate or occasional drinkers. They were tested on an apparatus with all the internal fittings of an automobile that appears to the driver to be passing along a winding tree-fringed road. Personality tests were made on the drivers and driving tests carried out both before and after the consumption of graded amounts of alcohol or placebos. The amount of alcohol consumed corresponded to 0.20, 0.30, 0.50, and 0.65 Gm. per kilogram of body weight. During the tests an automatic record was made of speed, tracking errors, curb bumpings, steering wheel and acceleration movements, brake applications, and gear changings. Samples of blood, urine, and breath were taken every half hour for alcohol estimation.

Tests on breath samples showed that the amount of alcohol in the breath, as estimated by the drunkometer and breathalyzer, gave good agreement with blood alcohol figures. The results showed a steady decline in driving skill with increasing alcohol consumption. There was a deterioration in driving skill of 12% when the blood alcohol level registered 80 mg. per 100 ml. Steering and tracking were also adversely affected, resembling the effects produced by fatigue. After ingestion of alcohol, extroverts drove on with maintained speed and many errors; introverts either slowed down appreciably or speeded up. The effect of the alcohol persisted for two hours. Age, sex, drinking habits, and driving experience showed no relation to individual differences in response to alcohol. Even the smallest amount of alcohol detectable caused measurable deterioration in skill.

Professor Drew said that he was in favor of chemical tests of urine or blood for determining whether a person who had indulged in alcohol was fit to drive. He said that it was impossible to set a level of alcohol at which everybody could be stated to be drunk. Clinical tests of drunkenness, tiredness, or lack of oxygen may be unreliable because a person can pull himself together for a while during the performance of the test. A definite level of blood alcohol should be set, above which a person should be considered legally unfit to drive. At the moment, all that the courts require is evidence that a person is sufficiently under the influence of alcohol to be unfit to drive. A critical blood alcohol level should be defined for legal purposes. Experience would show at what alcohol level drivers were getting involved in accidents, and the level could be lowered if necessary.

Lawyers and the press, however, are not in favor of convictions of drunkenness on the basis of blood alcohol levels. They say that while a high, low, or zero alcohol level is a guide to the court, most cases fall between, and personal idiosyncrasies are such that the courts would have little valid guidance. Adoption of a standard level would really mean that no one should consume any alcohol within a few hours of driving.

Freezing Point of Skin.—The determination of the freezing point of human skin is important to persons suffering from exposure in ice-cold sea water or arctic surroundings. Kestinge and Cannon determined the freezing point of the skin of the fingers, recording the temperature by means of a thermocouple of copper and constantan wire applied to the skin under several layers of adhesive tape (*Lancet* 1:11, 1960). The fingers were cooled by immersion in brine of the same composition as sea water, which freezes at −1.9 C, or by a cooling spray of a quickly evaporating solvent. Freezing was considered to have occurred when the finger was white and felt and sounded hard when tapped with a piece of wood and when the cooling curve revealed a sudden increase in temperature. Tests made on 11 subjects disclosed that the freezing point of skin is between −0.53 and −0.65 C. Repeated experiments on the same subjects caused hyperemia and tenderness of the fingers, followed by blistering and sloughing of the skin. These results show that, contrary to general belief, human tissues can freeze at the temperature of freezing sea water and that as a result they can sustain injury. It is important to provide sufficient protection to keep the skin temperature at more than 1 C (above water temperature) when immersion in freezing sea water occurs.

Serum Fatty Acids and Heart Attacks.—Many fatal heart attacks, while demonstrably due to ischemic heart disease, present no recent lesions in the myocardium or arteries to account for sudden heart failure. In a survey in which enzyme tests were used to elucidate the nature of these attacks, Enticknap also determined the serum fatty acid level (*Lancet* 1:32, 1960). The pathological diagnoses were simple coronary atherosclerotic narrowing or occlusion, fibrosis of the myocardium without recent change or thrombosis of the arteries, myocardial necrosis with or without accompanying coronary thrombosis, and arterial thrombus without gross myocardial change. In these four groups, comprising 50 cases, the serum fatty acid levels were 14.2, 12.6, 15.5, and 16.1 mEq. per liter respectively. The mean value was 14.7 mEq. per liter, whereas that of 57 controls of similar age was 9.9. The difference was highly significant. Most of the values higher than 17 mEq. per liter were from patients with ischemic heart disease. This suggests that high levels of serum fatty acids may be a factor in the causation of this condition.

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The analgesic was evaluated by a double-blind trial in patients suffering from joint pains due to osteoarthritis. Tablets containing aspirin, caffeine, and codeine (compound codeine tablets, B. P.) were used as a control. The results showed that the new drug and control did not differ significantly. Further tests were made with chlorthenoxazin and acetophenetidin, the analgesic action of which is equivalent to that of compound codeine tablets. During the trials, which lasted 18 months, no toxic effects from the new drug were seen. Its advantage over aspirin is that it does not cause gastrointestinal bleeding, and the lethal dose is much larger. In Britain, 177 deaths occur annually as a result of aspirin poisoning. Since the lethal dose of chlorthenoxazin in man is of the order of 1,000 tablets, the chances of suicide or accidental poisoning from it are remote.

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The number of deaths from all forms of tuberculosis was 4,785, or 11% less than in the previous year. The number of deaths from pulmonary tuberculosis decreased by 12%, but for the first time in many years there was a rise in the number of deaths from extrapulmonary tuberculosis. There were no deaths from respiratory tuberculosis in the group 9 to 14 years of age. Many more men than women suffered from tuberculosis. The rate per 1,000 population was 82 for men and 49 for women. Over 3,500,000 mass radiography examinations were made. These were responsible for picking muscle pattern more than a liver pattern. There were several indications that musculature was also involved sometimes in chronic alcoholism. Muscle necrosis with myoglobinuria was demonstrated in several patients. In rare cases there might also be necrosis of the calf musculature in chronic alcoholics. In four patients liver biopsy showed normal histological findings, without fatty degeneration, in spite of the fact that these patients had appreciable transaminase elevation. Probably liver cell necrosis, manifested in an increase in transaminase activity, was the earliest sign of liver damage in chronic alcoholism and preceded the fatty degeneration of the liver.

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The number of deaths from cancer, 94,017, was greater than in any previous year, the number of deaths of men exceeded the number of deaths in women by 6,095. The greatest increase in both sexes was in cancer of the lung, which accounted for nearly 33% of all the deaths from cancer in men but only 6% of such deaths in women. There were 188,630 deaths from diseases of the circulatory system and 73,669 from vascular lesions of the central nervous system, which together accounted for just over 50% of all deaths. There were 21,561 deaths resulting from accidents and violence.

Sarcolysin Peptides.—In 1956, the antimitotic, sarcolysin, was used by Larionov and other Russian workers for treatment of Hodgkin's disease and reticuloses. Since then, these workers have synthesized a number of peptides on the assumption that these may act as carriers of the chloroethylamino groups of nitrogen mustard and may be more effective in reaching the tumor site than sarcolysin itself. Larionov and Perevodchikova (*Brit. M. J.* 1:109, 1960) used the peptides of N-formyl-sarcolysin, which showed antitumor activity in mice and did not inhibit hemopoiesis as much as sarcolysin itself. Peptides of N-acetyl-sarcolysin and N-acetyl-sarcolysin-valine ethyl ester (asaline) were made, and asaline was given to 19 patients at the Institute of Experimental Pathology and Cancer Therapy in Moscow. A daily dosage of 1 to 2 Gm. was used. The only tumors in which asaline produced any regression were seminoma metastases, reticulosarcoma, Ewing's tumor, myelomatosis, and plasmocytoma. Partial regression occurred and relapses resulted within three months of stopping treatment. The effect on Ewing's tumor was only transient. Asaline was well tolerated and no depressant effect on hematopoiesis was observed.

Hypothyroidism and the Nervous System.—At a meeting of the Royal College of Surgeons in London, Prof. E. J. Wayne stated that reaction time was increased in 46 of 50 untreated patients with hypothyroidism and decreased in all patients who were treated. Dexamphetamine was found to shorten the reaction time in such patients. Prolongation of reaction time was thought to result from changes in cerebral function rather than in nerve conduction. Fifty-six percent of the patients complained of numbness and tingling, which occurred mainly during use of the hands or during the night.

Workers in Wayne's laboratory made an electromyographic study of this phenomenon and found that the median nerve was usually involved and, in addition to the paresthesia, there was often some motor paresis and slowing of conduction of the median nerve in the region of the wrist. The findings indicated compression of this nerve in the carpal tunnel, similar to that found in the carpal tunnel syndrome. Accumulation of myxedematous tissue under the flexor retinaculum is the cause of the compression. This impairment of conduction seemed to occur more in overweight persons, and it was relieved after treatment with thyroxin. Wayne suggested that many unnecessary operations for relief of the carpal tunnel syndrome might have been avoided if the patients were first examined for manifestations of hypothyroidism.

Amebic Dysentery.—Antibiotics have proved useful in treatment of amebic dysentery. Tetracycline, chlortetracycline, and oxytetracycline are almost equally effective in a dosage of 1 Gm. daily. Their main disadvantage is that the relapse rate is high and that they fail to prevent liver involvement. Powell and co-workers showed that their action is potentiated by such quinoline derivatives as chloroquine and diiodohydroxyquin (*Lancet* 1:76, 1960). They treated 125 Africans who had amebic dysentery with these drugs. The patients were divided into groups and treated with (1) chloroquine, diiodohydroxyquin, and suboptimal doses of tetracycline; (2) diiodohydroxyquin and suboptimal doses of tetracycline; (3) chloroquine and suboptimal doses of tetracycline; and (4) diiodohydroxyquin and chloroquine. Although addition of either chloroquine or diiodohydroxyquin alone to tetracycline had little effect, a combination of the two drugs with the antibiotic resulted in an immediate cure rate of 94%. The cure rate of a combination of diiodohydroxyquin and chloroquine was 60%. The use of chloroquine prevented liver complications. The rate of healing of rectal ulcers was slower when tetracycline was used in suboptimal doses, but the end-result was satisfactory.

Prolonged Survival of a Marrow Transfusion.—Reports have been made on patients afflicted with acute leukemia who have been treated with large doses of total body irradiation followed by marrow transfusions, but in none has the donor marrow survived for more than two or three weeks. Beilby and co-workers observed a patient in whom a marrow transfusion persisted after nearly 10 months although it resulted in the blood-group picture of a red cell chimera (*Brit. M. J.* 1:96, 1960). The patient was a woman who had had Hodgkin's disease for about five years and had received two courses of irradiation. After five months' treatment with chlorambucil there was evidence of marrow failure and, in spite of blood transfusions, the hemoglobin level decreased to 7.6 Gm.%, the leukocyte count to 25, and the platelet count to 5,000. The patient's condition was critical. From the sternum and ischia of her sister, 40 ml. of marrow was obtained, and after dilution, centrifugation, and removal of the fat, it was injected intravenously into the patient. It was estimated that about 1.1×10^{11} nucleated erythrocytes were transfused.

The patient started to get better on the next day and steadily improved. Three weeks later the hemoglobin level was 66%, the leukocyte count was 2,620, and the platelet count was 170,000. Sixteen weeks later the hematologic findings were within normal limits. The blood group of the patient and donor had been determined before the transfusion. Four months later there was evidence that the patient had developed new blood-group antigens identical with those of her sister. It was considered that these were due to the proliferation of the transfused marrow, although somatic mutation from irradiation could not be ruled out. The transfusion was responsible for the production of 24% of the patient's erythrocytes.

It is believed that this is the first example of prolonged survival of a marrow graft in a human being. This may have been due to the destruction of the patient's antibodies by repeated irradiation and treatment with chlorambucil.

Neurological Centenary.—The National Hospital, Queen Square, will celebrate its centenary from June 20 to 25. The occasion will be marked by neurohistorical presentations and a wide range of social functions. In addition, the hospital will extend a cordial welcome to neurologists, neurosurgeons, and others to participate in these activities. Those who wish further details can obtain them from Dr. Macdonald Critchley, National Hospital, Queen Square, London, W. C. 1.

Antibiotics and Staphylococcus.—According to Prof. Ronald Hare (*Practitioner* 184:80, 1960) it was not so much the appearance of antibiotics as the disappearance of treatment at home that created the current staphylococcic problem. In a well thought out paper he pointed out the fallacies in the widely disseminated view that in the act of becoming resistant to an antibiotic a Staphylococcus becomes more aggressive. Resistance is a result of a single mutation, whereas for aggression several mutations of a different sort would be required. In support of this thesis the author noted that, although antibiotic-resistant staphylococci may be present in noses of most inmates of a surgical ward, it is only those belonging to certain bacteriophage types that produce infection. This suggests that it is not ability to resist antibiotics as much as membership in certain bacteriophage types that confers pathogenic power on a Staphylococcus.

In England members of only three bacteriophage types (80, 75/77, and 47/53/75/77) are responsible for over 50% of the infections that occur in surgical wards while types 80, 52A/79, 71, and 7/47/53/54/75 are the predominant organisms causing infection in maternity wards. These epidemic strains produce most of the infections and are apparently endowed with sufficient aggressive ability to oust other strains of staphylococci that may be present in the noses of nurses or patients at the time they enter a hospital in which such epidemic strains are producing infection.

Although the resurgence of staphylococci within the last 10 years may have been due to the activities of certain special strains, it is difficult to believe that similar strains did not exist before then. Prof. Hare suggested that they were less of a problem before the introduction of antibiotics than they are today because of changes not in the parasite but in the treatment and surroundings of the host. Some of the new drugs, such as the corticosteroids, depress ability to resist infection. There is more surgical interference, and many of the operations are almost designed to increase the risk of infection in that they last a long time, involve the exposure of large areas of tissue, and necessitate the presence of many people. Furthermore the modern tendency is to concentrate virtually all the seriously ill persons in large wards that are in close proximity to similar wards, the whole enclosed within the walls of an enormous hospital. This is a very different environment from that of the private home, small cottage hospital, or nursing home where much illness was previously treated. An organism so well endowed as the Staphylococcus to take advantage of any opportunity of parasitizing the noses of normal persons and producing cross-infection has chances of causing mischief in a modern hospital that were denied to its ancestors.

Children and Colored Tablets.—The annual report of the health officer for Plymouth included an article by Drs. T. Forrest and Hugh Jolly on an investigation they made to discover which color is preferred by children. The purpose of the investigation was to find out whether there was any color which, used for medicinal tablets, would help to reduce the incidence of accidental poisoning in children. The investigation, which included 613 children 1 to 8 years of age, showed that bright colors were the most popular. Magenta was easily the winner, being chosen by 104 children, followed by pink (74), blue (66), orange (64), brown (61), white (52), black (45), and wine (44). The low position of white was attributed to the fact the children recognized the white ones as pills and not candy. The authors concluded that tablets should be white so they would be less likely to be mistaken for candy.

Home Confinements.—If the experience of Ilford, one of the numerous townships that make up Greater London, is typical of the country as a whole, English women prefer to give birth at home rather than in a hospital. According to Gordon and Elias-Jones (*Brit. M. J.* 1:52, 1960), of 336 mothers who had had at least one baby born in a hospital and one at home, 80% preferred home confinement, 14% hospital confinement, and 6% had no preference. Of the 269 mothers expressing preference for home confinement, 13 could give no reason for their preference. The remaining 256 gave 338 individual reasons for their choice. Of these, 228 referred to separation from home, husband, or family. Of the 48 who preferred hospital confinement, 9 could give no reason for their choice. The remaining 39 gave 49 reasons, of which the two most frequent were that they obtained more rest in the hospital (23) and that it was safer to have a baby in the hospital (11).

Academy of Forensic Sciences.—At a meeting last year it was decided to establish a British Academy of Forensic Sciences. This academy is now formally established. Its objects are to encourage the study, improve the practice, and advance the knowledge of the forensic sciences; to hold meetings; to publish such material as is calculated to further the objects of the academy; and to do all things that may widen, improve, and develop the education and knowledge of those engaged in the forensic sciences and of the public. The academy will have three main sections—law, medicine, and science. A research committee has also been formed. The secretary of the council of the academy is Dr. F. E. Camps.

Amateur Boxing.—In 1953, a medical welfare scheme was introduced by the London Amateur Boxing Association. The aim of the scheme was to ensure that only medically fit boxers were allowed to compete, that they received adequate medical attention, and that they ceased boxing for a sufficient time to allow them to recover from injuries, if any, sustained during a bout. Since the scheme was introduced there have been no deaths among amateur boxers in the London area. From 1946 to 1959 there were seven deaths due to boxing among amateurs in Great Britain. Since all were due to cerebral hemorrhage, resulting from a blow to the head and a fall backwards, the association introduced a resilient under cover to the ring. In two of the fatal cases the boxers were found to have very thin skulls. These are some of the facts produced in "Medical Aspects of Amateur Boxing" issued by the London Amateur Boxing Association.

From October, 1955, to April, 1956, there were about 300 tournaments, representing some 3,000 contests, under the control of the London Amateur Boxing Association. About 3,000 boxers were involved. There were no skull fractures, and injuries elsewhere in the body were few. One boxer suffered a spontaneous pneumothorax, another fractured a fibula, and there were 11 cases of fractured metacarpals. There was not a single case of fractured nose or serious ocular injury. Twenty-nine boxers who had suffered severe concussions or who had been knocked out more than once were picked out for special study. Their ages ranged from 17 to 26 years. The electroencephalogram was normal in all, and neurological abnormalities were few. Three had retrograde amnesia of up to one hour, and in seven the post-traumatic amnesia lasted from one-half to three hours. The maximum period of unconsciousness was one-half hour. The figures for the 1956-1957 season, when there were 4,350 contests, were similar. There were 60 knock-downs, and nine boxers were unable to continue a further round. There were two fractures of the hand, one of the thumb, and two of the nose. There were five general injuries, such as sprains and abrasions. Facial cuts totaled 57. Seventeen boxers were referred for neurological and electrocardiographic examination, and all results were negative.

In an introductory chapter, called Boxing and Health, Dr. J. Sharp Grant pointed out that although thousands of amateur contests take place every year in Great Britain, there are few serious injuries—far fewer, proportionately, than in rugby or association football or in other athletic events. In his opinion, the physical training, road work, and moderation in smoking and drinking required of a conscientious boxer lead to physical fitness and good health. As a deterrent to juvenile delinquency it can play an important part by being the outlet for psychopathic traits—such as aggressiveness and feelings of inadequacy and inferiority.

Phencyclidine in Anesthesia.—Phencyclidine (Sernyl) is the most potent general analgesic agent which has been used in clinical medicine, according to M. Johnstone and co-workers (*Brit. J. Anaesth.* 31:433, 1959). They used the drug in 42 patients who underwent herniorrhaphy, hemorrhoidectomy, cholecystectomy, mastectomy, thyroidectomy, and prostatectomy. It was highly effective for pain arising in skin, subcutaneous tissue, muscle, bone, joints, pelvic floor, and perineum, but it did not give complete relief from pain arising in the peritoneum, celiac plexus, kidney, and testis. It has advantages over other sedatives and analgesics as it does not depress cardiovascular and respiratory functions and it can be safely used in treating elderly patients when opiates and other agents are contraindicated. Another advantage is that doses sufficient to permit such painful operations as hemorrhoidectomy or skin grafting fail to cause any depression of pharyngeal and laryngeal reflexes, thereby eliminating the risk of respiratory obstruction from anatomic causes.

The usefulness of the drug, however, is limited by the excitation which it sometimes causes and which may persist for 12 hours after a single dose. This excitation is said to have a disturbing resemblance to acute toxic psychoses, but it has not been encountered in elderly patients. Phencyclidine is, therefore, considered a safe and effective analgesic agent in the following circumstances: (1) as the sole anesthetic agent for elderly hospitalized patients undergoing relatively superficial operations and endoscopies when anesthesia with conventional agents is considered inadvisable; (2) postoperatively as it provides excellent relief from pain arising in skin, muscle, bone, perineum, and pelvic floor (excitement is suppressed by the previous administration of halothane-oxygen); and (3) as a useful supplement to conventional anesthesia in operations involving the perineum and pelvic floor.

Ambulation After Hematemesis.—Patients bleeding from a peptic ulcer who are mobilized as soon as massive hemorrhage stops did as well as those kept in bed, according to Pollard and Summerskill (*Brit. M. J.* 1:171, 1960), who investigated the problem in a series of 66 patients. Half of them were allowed to sit out of bed for three hours on the day after bleeding ceased and were ambulatory all day by the third day. The other 33 were kept in bed for a week after the bleeding ceased. No ill effects were noted as result of early ambulation. Rapid mobilization was particularly advantageous from the social and economic aspects. The saving in hospital beds alone in this series of patients was calculated to have been equivalent to a saving of $9,100 during the course of the year covered by the investigation.

Control of Lipemia in Diabetic Children.—The effects of feeding unsaturated fats on the serum lipid levels were studied by H. B. Salt and coworkers (*Lancet* 1:71, 1960) in 13 diabetic children whose ages ranged from 2 to 14 years and in whom the condition was being controlled with insulin. Eight were given an emulsion of sunflower-seed oil which led to a lowering of serum β-lipoprotein, esterified fatty acids, phospholipid, esterified cholesterol, and triglyceride concentrations to below the control levels. Five were given a diet in which most of the usual (animal) fat had been replaced by corn oil. The isocaloric change from the control to the corn oil diet led to a decrease in esterified cholesterol and β-lipoprotein to about 60% of the initial control levels, esterified fatty acid levels to about 75%, and unesterified cholesterol and phospholipid levels to about 80%. Although the mechanism whereby unsaturated dietary fat lowers the level of serum β-lipoprotein is not clearly understood, the authors suggested that their observations indicate that a transfer of lipid from β-lipoprotein to α-lipoprotein might be an intermediate stop, since the α-lipoprotein level was seen to increase transitorily at the time when the β-lipoprotein level was being lowered.

In two patients on the corn oil diet the effects of lessening the dosage of insulin were observed. The cholesterol and phospholipid levels remained low, but the diet did not prevent an increase in triglyceride, esterified fatty acid, and the chylomicron lipid fractions. This finding has a special significance for the diabetic in whom the disorder of carbohydrate metabolism, unless constantly well controlled, leads to an increase in cholesterol, phospholipid, and β-lipoprotein levels under usual dietary conditions. The hyperlipemia of diabetes was similar to that preceding atheroma in older nondiabetics and might play an important part in the causation of the vascular complications of the disease. Although hyperlipemia can no doubt be prevented by perfect control of the diabetes with insulin, such control is rarely, if ever, maintained over long periods. It was therefore urged that, as an additional controlling measure, a diet rich in unsaturated fat deserves long-term trial.

Dumping Syndrome.—In the *British Medical Journal*, Jan. 16, Dr. Le Quesne and co-workers set out to estimate changes in plasma volume and to discover why some patients have dumping symptoms with a given decrease in plasma volume while others do not. By applying tourniquets around the thigh to simulate loss of blood, they were able to show that those patients who experienced symptoms of dumping, but who had a small decrease in plasma volume, were sensitive to similar small changes produced by thigh tourniquets. Likewise, patients with large changes in plasma volume but who did not experience dumping were immune to the effects of thigh tourniquets. Results of other workers showing that dumping can occur without any significant change in plasma volume need explanation, as does the fact that balloon distension alone can cause characteristic dumping.

The authors showed that a change in plasma volume was directly proportional to the rate at which the blood sugar level increased in the first 10 minutes after oral ingestion of a standard glucose drink. One explanation was that, in the patient who experienced dumping, gastric emptying was rapid and therefore glucose passed quickly into the jejunum and was absorbed rapidly. The authors suggested that the rapid increase in blood glucose level was the cause rather than the effect of dumping. They argued that this quick increase in blood sugar level interfered osmotically with the fluid shift across the jejunal epithelium and caused a greater and more rapid transfer of fluid into the lumen of the intestine. To account for the great variation in the frequency of dumping, they suggested that some people are metabolically different from others in that they do not metabolize blood glucose rapidly and therefore develop a high concentration shortly after ingesting a carbohydrate meal. Patients with dumping symptoms were given insulin in varying doses and found that the changes in plasma volume were significantly decreased as a result. They also found that dumping symptoms were diminished by the administration of insulin before a meal.

Investigations, however, did not show directly that there was a rapid shift of fluid across the jejunal mucosa in patients who had a gastrectomy. The evidence was by inference from the change in plasma volume. This change could be due to pooling of blood in the venous system instead of actual loss of fluid across the jejunal wall. If a high blood sugar level is one of the factors in inducing dumping, it could be reproduced experimentally, in those patients who did not have symptoms, by intravenous administration of glucose at the same time as the meal was taken. There are a few practical steps that may be taken to prevent or diminish dumping. The incidence was less after a Billroth 1 than after a Polya gastrectomy, and it was less after the Polya operation if a narrow stoma was made. If symptoms are incapacitating after a Polya gastrectomy, it may be justifiable to convert it to a Billroth 1, though this is not always successful. A patient who experiences dumping symptoms after operation should be reassured that they will disappear, as only 5% are affected after two years. He will gain relief if he lies down when eating and if he takes fluid between instead of during meals. No drugs influence the symptoms in any way.

Teaching Social Medicine.—In a report published by the British Medical Students' Association on teaching social medicine in 17 British medical schools, it is noted that in three schools this subject is not taught at all. The number of lectures given ranged from 0 to 60. Thirteen schools arranged visits as part of the social medicine course which included trips to industrial works, canteens, public health centers, geriatric units, special schools, and special clinics. The subject matter taught was based on medical sociology, epidemiology, and National Health Service administration. Only a minority of schools included any mention of international health service organization. In five schools no examination of any kind was held in social medicine, and two held a class or terminal examination on completion of the course. In 10 schools social medicine formed a part of the degree examination. On the subject of examinations, the association believed that only when an examination was held in a particular subject was it guaranteed that most of the students would pay sufficient attention to the teaching and thus benefit from it.

Student opinion on the subject was obtained from 15 medical schools. In 10 schools the view was that the student should be given an insight into those social aspects which affected the health of the community. In the remainder the opinion was that social medicine ought not to be given a prominent place in undergraduate education and that the different aspects taught could be integrated with other subjects. The final recommendation was that social medicine should be taught as an individual subject but that the course ought not be too detailed. More emphasis, however, should be placed on the social aspect of clinical cases in the wards. In spite of the views expressed about the importance of examinations as a stimulus to interest, the final recommendation was that the standard of knowledge required ought not to be such as would make social medicine a subject in the final examination. As a compromise, the view was expressed that an integrated examination in social medicine and infectious diseases would meet the requirements.

Teaching of Psychiatry.—Teaching of psychiatry and psychological medicine was the subject of another report published by the British Medical Students' Association. Of the 17 medical schools covered by the report, 6 indicated that no teaching in normal psychology was given. In the teaching of psychiatry the number of lectures given ranged from 7 to 32, excluding lectures on normal psychology. In most of the schools lecture-demonstrations were arranged, but the number of compulsory ward rounds varied from 0 to 16. Nine of the schools indicated that no formal inpatient ward rounds were arranged. Attendance at psychiatric outpatient clinics ranged from 0 to 26. In three schools arrangements were made for students to reside in psychiatric units, but in no school was there a period of compulsory attendance as a student in a mental hospital or unit.

A new scheme for the teaching of psychiatry was introduced in the University of Sheffield last autumn. In the preclinical period, 10 lectures on psychology are given by the head of the psychology department, and three to six lecture-seminars are given on normal and abnormal psychology. In the clinical course there is an introductory lecture during the introductory clinical course, followed by two social psychiatry seminars as part of the social medicine clerkship in the fourth year. In the fourth year there is also a period of clerkship in the department of psychiatry as part of a neuropsychiatric clerkship of one month, and in the fourth and sixth years there are weekly ward rounds by the professor of psychiatry in the medical wards with junior and senior medical clerks. In the fifth year there are two lectures to students doing their obstetrics, and in the sixth year there are weekly lecture-demonstrations in mental hospitals.

There is to be an obligatory question on psychology in the final examination and a voluntary examination and prize examination in psychiatry in the fifth year. The final examination in medicine is to become an examination in medicine, including psychiatry, and the professor of psychiatry is to examine with the professor of medicine. There will be one or two obligatory questions in the written medical examination and probably an obligatory clinical examination.

CORRESPONDENCE

STATEMENT OF AMERICAN CANCER SOCIETY ON CIGARETTE SMOKING AND LUNG CANCER

To the Editor:—The following statement was approved by the board of directors of the American Cancer Society on Jan. 21, 1960.

"In 1959 the death rate from lung cancer among men in the United States was over 10 times as high as it was in 1930. The disease is now one of the most common and most lethal of all forms of human cancer. This tremendous increase in number of deaths and the reported association of cigarette smoking with lung cancer has led the American Cancer Society to pursue an aggressive program of research on lung cancer and to disseminate new evidence bearing on the subject to the medical profession and to the public.

"In October, 1954, the board of directors of the American Cancer Society declared that 'the presently available evidence indicates an association between smoking and lung cancer.' In November, 1957, the board reviewed the report of the study group on smoking and health and agreed with its conclusions that 'the evidence of a cause-effect relationship is adequate for considering the initiation of public health measures.'

"The board now believes that it has a further responsibility both to the medical profession and to the general public to state that in its judgement the clinical, epidemiologic, experimental, chemical, and pathological evidence presented by the many studies reported in recent years indicates beyond reasonable doubt that cigarette smoking is the major cause of the unprecedented increase in lung cancer. The board further believes that all organizations and agencies concerned with cancer have a responsibility to formulate programs of action based on this information in order to reduce the incidence of this largely preventable disease.

"The strong association between cigarette smoking and lung cancer has been established by an extraordinarily large amount of evidence. Twenty-eight studies have indicated that a history of smoking is more common among lung cancer patients than among those without the disease. Three follow-up studies of smokers and nonsmokers have demonstrated that the death rate from lung cancer among cigarette smokers is about 10 times as great as among nonsmokers. Epidemiologic studies indicate also that cigarette smoking is associated with about 75% of all cases of lung cancer. The incidence of the disease increases with the amount of cigarette smoking, and no threshhold below which lung cancer will not occur has been identified.

"The fact that the association is one of cause and effect is well supported by several types of evidence. For example, in experiments condensates of tobacco smoke have produced cancers on the skin of mice and rabbits. After experimental exposure of mice to tobacco smoke or its condensates, abnormal cellular growths have been reported on mouse bronchial epithelium, in tissue cultures, and on the cervix. Cilia, one of the lung's major defenses against inhaled particulate matter, have been shown to be paralyzed by tobacco smoke. At least 10 chemical agents that have been identified in cigarette smoke have caused the development of cancer in laboratory animals. Studies of pathological changes in bronchial tubes of smokers have shown that abnormal cellular changes in the bronchi of the lung increase in degree and frequency as the amount of cigarette smoking increases and that in nonsmokers these changes are scarcely present at all.

"Some studies indicate that cigarette smoking is not the only causative factor in lung cancer. Certain occupational causes are recognized, and other factors such as air pollution have been implicated. The evidence indicates that the development of most cases of lung cancer is a complicated process in which cigarette smoking is the major controllable, though possibly not the only, factor. The existing evidence does not support the alternative hypotheses suggested to explain the exceptionally high degree of association of cigarette smoking with lung cancer.

"In presenting its conclusions the American Cancer Society recognizes that cigarette smoking is a personal habit and that the risk involved is at the option of the individual. The Society, nevertheless, believes that it has a responsibility to do everything possible within its established policies to reduce the alarming and rapidly increasing number of deaths from lung cancer. To that end the Society plans to continue support of research on lung cancer and to promote the widespread dissemination of information regarding causes and prevention of the disease to physicians and to the public with primary initial emphasis on teen-agers."

WARREN H. COLE, M.D.
840 S. Wood St.
Chicago 12.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Catheterization of the Left Heart by the Percutaneous Femoral Route: Technique and Results in Acquired Cardiopathies. M. Mouquin, E. Chartrain, J. Y. Pierron and G. Bacquet. Presse méd. 67:2081-2084 (Nov. 28) 1959 (In French) [Paris].

The technique and advantages of catheterization of the left heart by way of the percutaneous femoral artery are described. The authors have performed 200 such catheterizations without considerable accident. They have used the method successfully in children even younger than 10 years of age, but have not used it in patients over 55 years, since it is contraindicated in older patients. Catheterization of the left heart is also contraindicated in patients with a severe cardiac or kidney condition or with fever and in those who are being treated with anticoagulants or show a positive iodine test. Treatment with antibiotics 2 days before catheterization is advisable. An iodine test is indispensable before the angiocardiography. The authors experienced failure in about 10% of the cases, but in the last 100 patients of the series observed, there were only 2 failures.

The authors point out that the main advantage of this method is to make possible a method of angiography that can provide data so far unobtainable by venous angiography. Catheterization of the left heart is especially useful in doubtful cases of mitral insufficiency in which commissurotomy is debatable.

Lipoproteins, Cholesterol and Serum Proteins as Predictors of Myocardial Infarction. I. H. Page and L. A. Lewis. Circulation 20:1011-1027 (Dec.) 1959 [New York].

The normal variability of lipoproteins and Cholesterol levels was studied in 6 healthy women, ranging in age from 20 to 50 years. Tests were made at weekly intervals for about 5 months. In 3 of the women the serum total cholesterol levels were stable, and in the other 3 much less so. Single measurements of cholesterol or lipoproteins can be dangerously misleading.

The authors also report the results of a 7-year study on 107 "normal" Cleveland executives who were examined annually; myocardial infarction developed in 11, and angina pectoris or coronary insufficiency in 6. This provided "before" and "after" data in the same patient. Little change in lipid levels was associated with these events, when the changes occurring during the first 2 months after infarction were ignored.

Serum lipoprotein and electrophoretic protein patterns were studied in 84 patients shortly after myocardial infarction and in 66 repeatedly, at 5-to-10-day intervals, for 3 or 4 weeks. Four of the patients were studied after a second infarction as well. Most patients within a week of infarction showed increased beta and gamma-2 globulins with moderate increase in fibrinogen. Some exhibited increase in –S 20-25 and in low-density (–S 40-70 and 70-400) lipoproteins as well as in the electrophoretic changes. Finally, a few had a progressive rise during the 2 or 3 weeks after infarction in low-density lipoproteins. Serum cholesterol value was higher in young male patients with infarction than in the oldest age group with infarction. Similar age trends did not occur in women. After a second infarction, the low-density lipoproteins increased just as after the first one. The electrophoretic and lipoprotein changes after each infarction were strikingly similar. There was little correlation, however, between the lipoprotein pattern and the severity of the infarction, as measured by the electrocardiographic and clinical evidence. Increase in gamma-2 globulin was usually greatest in patients with the most extensive myocardial damage.

Three months to 10 years after infarction the range of lipoprotein values tended to fall within normal levels, but continued to exhibit slight preponderance toward values higher than the mean "normal." As a group, patients with coronary atherosclerosis with myocardial infarction exhibit slightly elevated cholesterol and lipoprotein values.

Electrocardiogram in Tetanic Patients. L. R. Perez. Rev. Clín. españ. 74:20-25 (Oct. 15) 1959 (In Spanish) [Madrid].

The cause of death in tetanus is not always the asphyxia, which originates the functional spasms of the respiratory muscles, or the pulmonary complications or the hyperpyrexia; death may also be

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The place of publication of the periodical appears in brackets preceding each abstract.

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caused by myocardial involvement. The author reports on the results of the electrocardiographic study of 12 patients with tetanus, as part of an investigation stimulated by his observation of more than 70 tetanic patients. The analysis of the electrocardiograms taken periodically during the course of the disease revealed that in all the patients studied the electrocardiographic alterations occurred with identical characteristics. The most constant alteration was the flattening of the T wave in all the leads. Although the intensity of the alteration varied in the various leads, it was always more intense in lead 3 where the T wave appeared almost always inverted. Less constant was the widening of the QRS complex. These changes were not correlated to the intensity of the tetanic symptoms or to their complications. They appeared as early as the third day after the onset of the disease and steadily increased in intensity, lasting even for some time after the recovery. These findings raise the problem of determining whether the electrocardiographic changes correspond to a functional disturbance, to a metabolic alteration, or to a myocardial lesion caused by the toxin of tetanus. It is recommended that the possibility of a myocardial lesion be taken into consideration for the purpose of both prognosis and therapy in patients with tetanus.

Determination of Uropepsin as an Aid in the Differential Diagnosis Between Gastroduodenal Ulcer and Neoplasm of the Stomach. H. Cesnik. Arch. klin. Chir. 293:1-9 (no. 1) 1959 (In German) [Berlin].

In more than 1,000 determinations of uropepsin in patients with various diseases, it was noted that the urine of those with gastroduodenal ulceration generally had increased uropepsin values, whereas in those with gastric carcinoma the uropepsin levels were below normal. The possible differential diagnostic value of this difference in the uropepsin content of the urine was investigated at the surgical clinic of the University of Graz, in Austria, by the method of West, Ellis, and Scott. Comparative tests on the uropepsin excretion were made in 220 patients. The 50 persons in this group serving as controls were mostly patients who were about to be discharged from the hospital after a minor operation or accident. Of the 150 patients with gastrointestinal lesions, 50 had duodenal ulcers, 50 had gastric ulcers, and 50 had gastric neoplasms, all but 3 of which were malignant. The 5th group of 20 patients had been hospitalized because a gastrointestinal disorder was suspected.

The average uropepsin excretion in patients with duodenal ulcers was 201 mg. per 100 cc.; in patients with gastric ulcers, 144 mg. per 100 cc.; and in patients with gastric neoplasms, 69 mg. per 100 cc.; in persons without gastric lesions it was close to 100 mg. per 100 cc. The uropepsin values were above normal in 90% of the patients with gastroduodenal ulcers, and below normal in 90% of those with gastric neoplasms. A difficulty in the comparison between the pathological and normal values arises from the fact that, although in the individual patient the values are rather constant, they vary considerably from patient to patient. For this reason, the diagnosis of ulcer or carcinoma cannot be based exclusively on the uropepsin values, but the author feels that the uropepsin test is a valuable addition to the differential diagnosis for patients with gastroduodenal disorders.

Relationship Between Plasma and Extracellular Fluid Volume Depletion and the Antihypertensive Effect of Chlorothiazide. I. M. Wilson and E. D. Freis. Circulation 20:1028-1036 (Dec.) 1959 [New York].

The discovery of the antihypertensive action of chlorothiazide raised questions as to its mechanism of action, such as whether the hypotensive response was caused by salt depletion or some other factor. The importance of plasma and extracellular fluid volumes in the mechanism of the antihypertensive effect of chlorothiazide is disputed. The authors made studies on 20 male hypertensive patients, without symptoms of congestive heart failure or edema, who were hospitalized and placed on a standard diet containing 1.5 Gm. of salt per day plus a supplement of 3 Gm. of salt in tablet form. This supplied a sodium intake of approximately 75 mEq. per day. Most of these patients were under treatment with other antihypertensive agents, which were continued during the period of study. A 4-day period for acclimatization to the diet was instituted in order to obtain stabilization of body weight and electrolyte excretions as well as average basal blood pressure readings. Determinations of plasma and extracellular fluid volumes, serum electrolyte concentrations, and serum bicarbonate levels were carried out on the 5th day. Each patient was then given 500 mg. of chlorothiazide twice daily, and the studies were repeated after 3 to 8 (average, 6) days.

Plasma and extracellular fluid volumes decreased during the early phases of treatment. This was accompanied by a reduction of arterial pressure and body weight. Sodium losses could be accounted for on the basis of depletion of the extracellular fluid volume. Restoration of plasma volume, either with or without partial replenishment of sodium, reversed the antihypertensive effect of chlorothiazide. Withdrawal of chlorothiazide after 3 to 7 months of treatment was followed by an elevation of plasma volume and of the blood pressure. Significant reductions of plasma volume and body weight were not found after 6 months, and of extracellular fluid volume after 12 months, of therapy, even though the blood pressure remained reduced. However, the latter may not be a valid criterion of drug activity after long-term modification of the blood pressure level. The only significant change in serum electrolyte concentration was a reduction in serum potassium level. Serum bicarbonate levels were not altered. It is suggested that the decrease in plasma volume is an important factor in the initial antihypertensive effect. Reduction in tissue pressure, secondary to extracellular fluid volume depletion, could also contribute to this response.

Evaluation of Chlorothiazide Alone in the Treatment of Moderately Severe and Severe Hypertension. F. A. Finnerty Jr., J. H. Buchholz, J. Tuckman and others. Circulation 20:1037-1042 (Dec.) 1959 [New York].

The authors compared the effectiveness of alternate 6-month courses with chlorothiazide medication alone and with standard antihypertensive therapy in 11 patients with severe hypertension and in 30 patients with moderately severe hypertension. The results obtained were then compared with the effects of a 6-month period of treatment during which the patients received both chlorothiazide and standard antihypertensive therapy.

It was found that neither the administration of chlorothiazide alone nor the administration of ganglionic-blocking agents plus reserpine constituted effective treatment in the 11 patients with severe hypertension. However, the addition of chlorothiazide to ganglionic-blocking agents plus reserpine reversed the accelerated phase of hypertension in each of these patients. Once papilledema had cleared and retinal hemorrhages had regressed, it was possible to substitute hydralazine or veratrum for the ganglionic-blocking agents in these patients.

Chlorothiazide alone and veratrum or hydralazine plus reserpine were found effective in controlling the blood pressure in about half of the 30 patients with moderately severe hypertension. The addition of chlorothiazide to either of these agents resulted in satisfactory control of the arterial pressure in all the patients with moderately severe hypertension. Once a hypotensive effect had been attained with veratrum or hydralazine, these agents could be withdrawn, and antihypertensive therapy continued with reserpine plus chlorothiazide.

Stress Ulcers in the Stomach. I. M. Breckenridge, E. W. Walton and W. F. Walker. Brit. M. J. 2:1362-1364 (Dec. 19) 1959 [London].

Six cases of acute gastric erosions are reported, in which the ulcers developed, after exposure to various forms of stress, in patients previously eupeptic, none of whom had been receiving salicylate treatment. The disease was fatal in the 6 patients; hemorrhage occurred in 5. The gastric ulceration followed cerebral hemorrhage in 2 patients, diffuse encephalomyelitis in 1, fracture of a long bone in another, and operation for carcinoma in 2. The patients were over 50 years of age, with the exception of a 26-year-old woman who had developed encephalomyelitis during pregnancy. In the 4 patients for whom microscopic examination was available, the ulcers were sharply demarcated and presented an area of necrosis with little or no cellular reaction, with no evidence of healing. The ulcers were regarded as acute and between 1 and 7 days old.

The occurrence of gastric erosions after such diverse forms of stress recalls the association between peptic ulceration and adrenocortical hormones, which was suggested by Selye in 1936 and which is generally recognized at present. Though there is ample evidence to connect the neuroendocrine system with the development of stress ulcers, the exact mode of production is unknown. Antacid therapy should be considered whenever a trauma, an operation, or cerebral lesions may initiate the gastric erosion sequence.

Treatment of Hypertension: A 23-Year Follow-Up of 453 Patients with a Selected Review and Report of Current Experience. R. S. Palmer. J. Chron. Dis. 10:500-512 (Dec.) 1959 [St. Louis].

This is the fourth and final report on 453 medically treated patients with hypertension, since there are now only 79 survivors. The majority were seen first in the years 1935-1940. No new patients have been added to the series since 1941. Survivals over the years demonstrated the usefulness of the original classification into the following grades: grade 1, including patients with hypertension, but without organic changes or functional failure; grade 2, patients without functional failure, but with organic changes in one or more of the 3 vital areas—head, heart, or kidneys; grade 3, patients with organic changes plus functional failure in one or more vital areas; and grade 4, patients with the clinical syndrome of malignant hypertension, the diagnostic sign of which is papilledema. Cardiovascular renal disease was the cause of death in 75 to 90% of the hypertensive patients (as compared with 50% for the general population) and appears earlier in life with each rise in grade of hypertensive disease.

It is safe, cheap, and often possible to control the blood pressure level by diet plus phenobarbital in grades 1 and 2, and sometimes it is possible in grade 3. Drugs are easy to prescribe and are far more easily accepted by the patient than is restriction in diet. Rauwolfia and its fractions or derivatives are slightly, if at all, more effective than phenobarbital and have more side-effects. The chief use of rauwolfia is as a tranquilizer, rendering acceptable more rigorous drug treatment. Chlorothiazide is a substitute for salt restriction; the bulk of the evidence indicates that its mode of action is diuretic, depleting the body of salt and water; the effect of years of use on the kidneys and other organs and tissues awaits further observation. Since chlorothiazide may cause a rise in uric acid and muscle and joint pains, use of small doses is effective and recommended; it should be combined with small doses of ganglionic-blocking drugs in grade 3 patients with actual or threatened congestive heart failure, and used alone in less severe grades with high blood pressure levels. Grade 4 patients, with clinically malignant hypertension with papilledema, require every resource of diet and drugs to control the blood pressure level, which by itself in this condition is rapidly fatal.

The ease with which the blood pressure level is observed and the ease with which it is treated by a multitude of hypotensive drugs have misled many practitioners (and those who teach them) to neglect the equally important therapeutic problem of patients with hypertension, and also of the general population, namely, degenerative vascular disease. Patients with hypertension differ from nonhypertensives only by having the condition oftener and sooner. Degenerative vascular disease is related to age, hypertension, and unknown factors as well as to ingested animal fat, the latter fact having been known for 50 years. Evidence is presented that a basic treatment of all patients with hypertension is a low-salt, low-animal-fat diet.

Hereditary Spherocytosis. J. R. Meier. J. Louisiana M. Soc. 111:472-475 (Dec.) 1959 [New Orleans].

The subject of this study in hereditary spherocytosis was a 48-year-old man who was admitted to the Hotel Dieu in New Orleans in March, 1958, with severe right upper quadrant pain, nausea, and vomiting. He was well developed but poorly nourished, and showed a severe jaundice. He appeared to be acutely ill, exhibiting the complete form of spherocytosis, with long-standing anemia, splenomegaly, jaundice, cholelithiasis, and chronic leg ulcers. Cholecystostomy was performed, with removal of multiple pigment stones from an acutely inflamed gallbladder; the postoperative course was uneventful. In January, 1959, the patient underwent splenectomy, and the immediate postoperative course was complicated by a subdiaphragmatic abscess from which coagulase-positive Staphylococcus aureus was isolated. The patient was discharged on the 30th day after the operation. At that time the hemoglobin value was 10.6 Gm. per 100 cc., and the hematocrit was 36%.

The anemia in this patient, as determined by the hemoglobin concentration, was never severe except at 2 points, the first during the acute episode of cholecystitis and the second after the subdiaphragmatic abscess. At one point the patient had an apparent hemolytic crisis, with a further drop in hemoglobin value and marked bilirubinemia. During the entire duration of follow-up examination the reticulocyte counts followed an expected pattern, being highest just prior to splenectomy, and gradually returning to normal as the hemoglobin value rose. The platelet counts also fell to 50,000 per cubic millimeter at the time the hemoglobin was at its lowest level. After splenectomy, thrombocytosis occurred without evidence of the thrombotic phenomenon. At the last follow-up visit, the serum bilirubin level had returned to 1.5 mg. per 100 cc., and the clinical jaundice had subsided. The patient had regained 18 lb. (8.2 kg.), and his condition was markedly improved.

The patient's 2 children have spherocytosis, with characteristic laboratory findings but with a milder anemia. The inheritance of the disease cannot be traced back farther than one generation, owing to lack of laboratory studies on the patient's family.

Treatment of Alcoholic Cirrhosis with Ascites: A Study Based on Statistical Data of 449 Cases, Including 85 Survivals of Over Two Years. M. Levrat, R. Brette and P. Grandmottet. Arch. mal. app. digest. 48:1265-1293 (Nov.) 1959 (In French) [Paris].

The prognosis in decompensated alcoholic cirrhosis has changed during the last 10 years as a result of new therapeutic procedures and of changes in the physiopathological concept and the control of ascites. Four hundred forty-nine patients with alcoholic ascitic cirrhosis were hospitalized and observed between 1953 and 1958. The findings are analyzed in relation to 3 time periods: (1) before 1953; (2) from 1953 to 1956; and (3) from 1956 to 1958. The frequency of death during the first month of observation was 37% in period 1, 37% in period 2, and 27% in period 3. These frequencies show the spontaneous gravity of the disease, especially during period 2 when consumption of alcohol increased after wartime restrictions were lifted. The frequency of death during the first year of treatment decreased from 68% in period 1 to 56% in period 3. The circumstances of death also changed. Although the picture of terminal hepatic coma is still the most common, the occurrence of serous cachexia due to irreversible ascites has almost disappeared. Digestive tract hemorrhage is at present a more important cause of death and occurs in 20% of the cases, while only 11% of the patients succumb owing to complications without edematous elements.

The therapeutic procedures have included administration of delta cortisone (prednisone) combined with mercurial diuretics and intravenous perfusion with human plasma. Abdominal paracentesis was abandoned. Only 2 or 3 of 50 patients who were freed from ascites underwent paracentesis in addition to the medical treatment. The combined therapy is illustrated in the report on a 55-year-old patient with alcoholic ascitic cirrhosis and edema of the lower extremities, who during 20 years had consumed 2 liters of wine daily. The patient received an initial dose of 30 mg. of delta cortisone, which later was increased to 40 mg., combined with an intramuscular injection of mercurophylline every other day. Eleven perfusions of 400 cc. of plasma were given—2 or 3 per week. After 2 months of this treatment the patient was discharged in excellent condition. He was rehospitalized 4 months later, however, with ascitic jaundice after a new period of alcoholism, and died 10 days after readmission, in intense jaundice.

The authors recommend that the over-all therapeutic conduct in alcoholic ascitic cirrhosis include a hypercaloric, high-protein diet and the administration of corticosteroids and mercurial diuretics. If the results are not satisfactory within 15 to 20 days, plasma should be given in intravenous perfusion. The patient whose condition is serious from the start should receive the 3 therapeutic agents combined. Under this management the prognosis is that 50% of the patients become free from ascites, 25% survive more than one year, and 15 to 20% survive more than 2 years.

Cirrhosis of the Liver: A Study of Alcoholic and Nonalcoholic Patients in Boston and London. W. H. J. Summerskill, C. S. Davidson, J. H. Dible and others. New England J. Med. 262:1-9 (Jan. 7) 1960 [Boston].

Seventy patients, comprising 35 from Hammersmith Hospital, London, and 35 from Boston City Hospital, were studied. Information based on history, physical examination, pathological findings, and relevant investigations was obtained. In the Boston group, evidence of chronic alcoholism was mandatory for inclusion, whereas patients with a steady or excessive intake of alcohol or a history of malnutrition were excluded from the London series, the etiology of the hepatic cirrhosis in this latter series being cryptogenic. No patient was included if a diagnosis of hepatolenticular degeneration (Wilson's disease), hemochromatosis, cardiac failure, biliary obstruction, or ulcerative colitis had been established or if L. E. cells had been identified in the peripheral blood. Among the alcoholic patients in Boston, men predominated 2:1; working, domestic, and financial conditions were poor, and malnutrition was common, but a history of hepatitis was not frequent. In contrast, the nonalcoholic patients in London were mostly women (2:1); environments were not unusual, evidence of severe nutritional disturbances was rare, and previous hepatitis had been known in 11.

The prominent clinical features of patients in the cryptogenic group were usually related to portal hypertension, and episodes of hepatic precoma were common. The alcoholic patients, although frequently showing these abnormalities, could be separated from the cryptogenic group by the frequency of deep jaundice, fever, high neutrophil counts, and macrocytic anemia. Parotid-gland enlargement, gynecomastia, and Dupuytren's contracture were confined to the alcoholic group, and hepatomegaly was frequent. Splenomegaly, rather than hepatomegaly, characterized the nonalcoholic subjects. Serum albumin concentrations, although initially abnormal for both groups, often rose toward normal during improvement of the alcoholic patients with cirrhosis, but tended to change little in the nonalcoholic group. The globulin concentrations of the nonjaundiced, ascites-free patients were usually between 3 and 5 Gm. per 100 cc. in the London group, but below 3 Gm. per 100 cc. in the Boston group.

Pathological studies showed that the liver was small in the nonalcoholic and large in the alcoholic patients. Large and irregularly sized regeneration nodules were a feature of the nonalcoholic group, the picture resembling postnecrotic cirrhosis. Small and regular regeneration nodules were a feature of the alcoholic group, the picture resembling portal cirrhosis. In the Boston patients the liver cells showed increased amounts of fat and often necrosis—unusual findings in the London group. "Alcoholic hyalin" was confined to liver specimens from the Boston group. Relapses, usually with jaundice, after renewed ingestion of alcohol were common among the Boston patients and, although sometimes fatal, often responded dramatically to abstinence and a nutritious diet. The liver disease of the London patients was less dramatic, but *inexorable progress was the rule.*

Marked Enlargement of the Liver and Transient Ascites Associated with the Treatment of Diabetic Acidosis. H. D. Bronstein, P. A. Kantrowitz and F. Schaffner. New England J. Med. 261:1314-1318 (Dec. 24) 1959 [Boston].

The case of a 7-year-old girl with unusual juvenile diabetic acidosis is reported. The salient clinical features included unusually high insulin requirement, acute massive hepatomegaly, with rapid regression, and transient ascites. The acute hepatomegaly that developed during the correction of diabetic acidosis appeared to depend on 3 factors: the rapid administration of very high doses of regular insulin; the presence of a high blood sugar level; and the deposition of massive amounts of glycogen in the liver parenchyma, distorting cell structure as seen electron microscopically. Hepatic sinusoidal obstruction and reduced inactivation of antidiuretic substances by the glycogen-laden hepatic cells are suggested as an explanation for the transient ascites. The unusual clinical course in this case is presented as a complication in the treatment of diabetic acidosis. The brief report of it should encourage wider use of liver biopsy, with application of histochemical and electron-microscope techniques, to clarify further the pathological physiology of hepatomegaly in diabetic acidosis.

Considerations on Severe Carbon Monoxide Intoxication: Its Treatment, Especially by Neurovegetative Disconnection. L. Binet, H. Bour and S. Elosma. Presse méd. 67:2125-2127 (Dec. 5) 1959 (In French) [Paris].

Seventy patients with carbon monoxide intoxication were seen by the authors during the period from 1954 to 1956. Eleven of the 70 patients died. Six patients with severe intoxication were treated by artificial hibernation; 3 recovered, and 3 died. In 2 of the 3 patients that died, hibernation was started apparently on time, but was interrupted too early, and there was a relapse of coma; both patients died in hyperthermia. In the third patient that died, hibernation was started too late. In all 3 patients that survived, hibernation was started early and was maintained well beyond the recovery of consciousness. Some neuropsychic sequelae remained in one patient.

The authors point out that the difficulty of knowing the extent of anoxia in each case and the length of time that the patient has been exposed to toxic elements pose the fundamental problem in the treatment of carbon monoxide intoxication. Hibernation may be an effective remedy in cases of severe carbon monoxide intoxication on 2 conditions: (1) that it is started early, as, for instance, if coma persists despite first-aid help or when there are signs of persisting reflex disturbances or severe vasomotor disturbances; (2) that it is continued for some time beyond the recovery of consciousness. As for the indication for hibernation in carbon monoxide intoxication, the authors believe that the absence of response of consciousness to immediate treatment, high temperature, vasomotor disturbances, particularly reddish purple complexion, and the existence of a subacute pulmonary edema point out the importance of the manifestations of the central nervous system and the vasomotor disturbances that follow cerebral anoxia. This justifies a treatment based both on the increase of the caliber of the cerebral blood vessels, which is obtained with sympatholytic agents, and on a general decrease in the consumption of oxygen, which is obtained by refrigeration.

Potassium and Myocardial Energetics. P. Michon, A. Larcan and P. Gaucher. Semaine hôp. Paris 35:3289-3301 (Dec. 4) 1959 (In French) [Paris].

Nine patients with cardiac insufficiency of varied etiology received a potassium replacement therapy by intravenous perfusion. Potassium chloride was administered to 7 patients in a continuous perfusion of 500 cc. of isotonic dextrose solution, to which 2 ampuls of 20 cc. of hypertonic dextrose solution and 15 units of regular insulin were added. The dose of potassium chloride varied from 4 to 12 Gm., and the duration of the perfusion was approximately one hour for 4 Gm. of chloride. The treatment was controlled by electrocardiography, by the measurement of intensity-duration curves, and by the determination of potassium and sodium blood levels. Three urine specimens were collected, one 4 hours after starting the perfusion, the second at the end of 8 hours, and the third at the end of 24 hours. In the remaining 2 patients the potassium replacement was performed in 2 stages. The first stage consisted of the administration of potassium chloride in an isotonic sodium chloride solution without either insulin or hypertonic dextrose solution. In the second stage the perfusion of 250 cc. of 20% dextrose solution included 30 units of insulin. Both patients received 6 Gm. of potassium chloride administered in approximately 2½ hours. In this 2-stage treatment the electrocardiographic control and the urinary examinations were approximately the same as in the first method.

The main clinical features in both groups of patients, before starting the therapy, were moderate hypokaliemia, increased muscular rheobase, slightly increased or normal kaliuria, and decreased or absent natruria. In the 7 patients who received a one-step potassium replacement, the kaliemia increased by an average of 1 mEq. The change in natremia was light and difficult to interpret. The only change observed in the electrocardiogram took place in the T wave, which exhibited the aspect characteristic of hyperkaliemia. The changes in urinary elimination were not always consistent. Kaliuria increased in most patients; natruria increased in all of them within 24 hours after the start of the perfusion. In the 2 patients who received a 2-step treatment, the results were of the same type. The main characteristic of this 2-step technique was that in the second stage, when insulin was added to the perfusion, there was a sudden and considerable fall in the kaliemia level, a decrease in muscular rheobase, and a further decrease in the urinary elimination of potassium. All 9 patients experienced a feeling of well-being after the perfusion, regardless of the difference in the technique. The clinical picture improved, with regression of edema, disappearance of dyspnea, and, in some patients, disappearance of the gallop rhythm.

The authors conclude that the slight increase in kaliemia, together with the low level of kaliuria, indicates that the potassium ion had reached the intracellular sector. The results obtained with the association of insulin and hypertonic dextrose solution suggest that this association allows a more rapid intracellular penetration of the potassium ion. A slow, strictly controlled administration of potassium chloride is beneficial to patients with decompensated cardiac insufficiency.

Hereditary Hypophysial Diabetes Insipidus: Observation During Pregnancy and Description of Family. E. Enger. Tidsskr. norske laegefor. 79:1291-1294 (Nov. 15) 1959 (In Norwegian) [Oslo].

Diabetes insipidus is marked by polyuria and thirst. The hypophysial form may be secondary and due to disease or injury of the hypothalamico-hypophysial apparatus, or primary and due to a defect on genetic basis of the apparatus producing the antidiuretic hormone. The hereditary hypophysial type was recognized as early as 1841. In most of the families studied, the inheritance has been autosomal, dominant; a recessive sex-bound inheritance has also been described, with transmission of the gene by healthy women. Hereditary hypophysial diabetes insipidus is a lifelong condition with favorable prognosis. In a given family the disease manifests itself with about the same intensity. Enger reports on the first family in Norway with recorded hereditary diabetes insipidus, inherited as a clear-cut autosomal dominance. In all cases the syndrome appeared in early childhood. Of 21 persons in the second and third generations of the family, 11 have a pathological thirst. All drink from 2 or 3 to 12 or 13 glasses of water nightly. At an older age the symptoms may become less marked. In the case described in a pregnant woman of this family, there was greatly increased thirst during the first part of pregnancy. Administration of extract of posterior pituitary lobe improved the condition. In the last trimester of the pregnancy, and particularly during lactation, there was a remarkable reduction of thirst. After the lactation period ended, thirst recurred on the same level as before. Information about the nature and prognosis of the disease can remove unnecessary dread and embarrassment. Diagnosis is possible by simple means, and administration of extract of posterior pituitary lobe is effective in most cases.

The Pleural and Pulmonary Complications of Rheumatoid Arthritis. A. R. Horler and M. Thompson. Ann. Int. Med. 51:1179-1203 (Dec.) 1959 [Lancaster, Pa.].

Rheumatoid arthritis is now widely considered as a generalized disease, involving, in addition to the joints, various other tissues and organs, including the lungs and pleura. In the 2-year period from January, 1956, to December, 1957, inclusive, 180 patients with rheumatoid arthritis (52 men and 128 women), ranging in age from 18 to 78 years, were referred to one of the authors at the department of physical medicine from other clinics and wards of the Royal Victoria Infirmary in Newcastle upon Tyne, England. These patients were studied with regard to the existence of pleural and pulmonary lesions and questioned about previous chest illnesses; their hospital records were searched for evidence of former respiratory complications. Nine patients were found to have, or to have had, a pleural effusion for which no cause could be found other than rheumatoid disease; 8 of them were males. One other patient had roentgenologic evidence of a "honeycomb lung." The case histories of these 10 patients are presented.

The 9 patients with pleural effusion have been under observation for periods ranging from 14 to 100 months (average, 48 months), and there has been no evidence that any other disease process could have been responsible for the effusion. Special efforts were made to exclude pulmonary tuberculosis, bronchogenic carcinoma, and systemic lupus erythematosus. Two of these patients (both males) also had coincident parenchymatous lung lesions; they were nodular in one, and diffuse and fibrotic in the other. The pleural and pulmonary lesions developed in both patients sometime after the onset of arthritis. The other 6 male patients with pleural effusion had no evident lesions of the underlying lung. The appearance of the effusion was accompanied by an acute febrile respiratory illness related to the onset of the arthritis.

A review of the relevant literature has confirmed the view that pleural effusion complicating rheumatoid arthritis occurs predominantly in men. In the only female patient in this series, the effusions developed several years after the onset of the arthritis. The authors conclude that rheumatoid arthritis merits consideration in the differential diagnosis of pleural effusion, especially when the effusion occurs in middle-aged men and is associated with the recent development of joint symptoms.

Oral Antidiabetic Therapy. R. H. Williams, R. H. Pollen, D. C. Tanner and R. H. Barnes. Ann. Int. Med. 51:1121-1133 (Dec.) 1959 [Lancaster, Pa.].

The authors discuss the 4 orally administered antidiabetic drugs—tolbutamide, chlorpropamide, metahexamide, and phenethylbiguanide. The 3 sulfonylureas—tolbutamide, chlorpropamide, and metahexamide—presumably lower the blood sugar level by stimulating increased insulin secretion and by decreasing hepatic glucogenesis, particularly in the presence of insulin. They seem to have their greatest effect in patients who most nearly approach normality in the amount of assayable insulin in the plasma and pancreas; these tend to be elderly persons with stable diabetes of recent onset. A poor response is apt to be obtained in depancreatized patients or in diabetes that is unstable or of long duration, or requires large insulin doses, or is prone to produce keto-acidosis. There is no evidence that treatment with sulfonylurea compounds causes beta-cell exhaustion. Side-effects with tolbutamide have been few and mild. Chlorpropamide and metahexamide have caused side-reactions more frequently, and occasionally have produced jaundice of the cholestatic type, usually reversed upon cessation of treatment. Metahexamide has caused jaundice with sufficient frequency to preclude its further use. While metahexamide and chlorpropamide are more potent than tolbutamide, this higher potency seems to have advantage in only a small proportion of patients.

Guanidine and many of its derivatives have long been known to produce hypoglycemia, but interest has recently been centered on a condensed diguanidine, phenethylbiguanide (PEBG). Phenethylbiguanide inhibits certain oxidative enzymes of the Krebs cycle, particularly succinodehydrogenase and cytochrome oxidase. This produces: (1) an increase in anaerobic glycolysis with an increase in glucose uptake, and (2) a decrease in gluconeogenesis, liver glycogen, and hepatic glucogenesis. As a result, glucose disappearance from the blood increases, and its entrance from the liver decreases, both factors contributing to hypoglycemia. This biguanide may lower the blood sugar level in all types of diabetes, but the greatest effect is observed in those with the mild, stable type. Combined with insulin, it produces smoother control in patients with unstable diabetes. In some subjects, chiefly with the stable type of diabetes, better control is obtained with the biguanide plus a sulfonylurea than with either drug alone. The high incidence of side-effects, even though rapidly reversible, has limited the extent of usage of phenethylbiguanide. Tolbutamide, chlorpropamide, and phenethylbiguanide all have value in the treatment of some diabetics. New orally effective compounds must be evaluated objectively, their effects being noted not only on the levels of sugar in the blood and urine but also on various phases of the metabolism of carbohydrates, fats, and proteins, as well as on the general health with prolonged usage.

Resistance to Ketosis in Obese Subjects. A. Kekwick, G. L. S. Pawan, T. M. Chalmers. Lancet 2:1157-1159 (Dec. 26) 1959 [London].

The authors tested the following 2 concepts of the resistance of obese persons to ketosis: (1) that the obese may utilize or excrete ketone bodies (acetone, acetoacetic acid, and beta-hydroxybutyric acid) faster than the nonobese, and thus prevent their accumulation in the body; (2) that the obese may not form ketone bodies so rapidly. To test the first concept, sodium beta-hydroxybutyrate was given to 6 obese and 6 nonobese persons. After intravenous injection of 30 mg. of this ketone body per kilogram of body weight, the rate of its disappearance from the blood was found to be the same in the obese as in the nonobese persons. Less than 1% of the injected dose was excreted in the urine; the amount excreted was the same in the 2 groups. Hence, the first concept—that the resistance to ketosis in obese persons results from their greater ability to excrete ketone bodies or to utilize them metabolically—does not appear to be tenable.

To test the second concept—that the rate of production of ketone bodies is less in the obese, an attempt to induce ketosis was made in 14 obese and 8 nonobese persons by giving them a diet providing 1,000 calories, of which 90% was supplied in the form of fat. In the nonobese persons the development of ketonemia and ketosis was preceded by a fall in the fasting blood sugar concentration. In the obese persons placed on this diet, there was no such fall, or it was small; ketosis to any significant degree did not develop. Taken in conjunction with the first experiments, these results suggest that resistance to ketosis in the obese results from a diminished production of ketone bodies. Reasons are given for believing that net conversion of fat to carbohydrate took place in both groups. It is suggested that obese persons may be able to produce more carbohydrate from nonprotein sources, i. e., from fat, than nonobese persons.

SURGERY

Diagnostic and Functional Evaluation of Candidates for Coronary Endarterectomy. A. A. Kattus, W. P. Longmire Jr., J. A. Cannon and others. A. M. A. Arch. Int. Med. 104:870-885 (Dec.) 1959 [Chicago].

The authors report on 23 patients with coronary occlusive disease, who had been referred or had presented themselves for consideration of surgical treatment at the University of California Hospital in Los Angeles. These patients had incapacitating angina pectoris and were evaluated from the point of view of establishing the diagnosis of coronary occlusive disease and of determining its severity. Electrocardiograms disclosing nonfixed ST-segment depression, either at rest or after exercise, proved to be a highly reliable indication of extensive occlusive coronary disease, usually involving more than one major arterial branch. In patients having normal resting electrocardiograms, the positive Master two-step test was reliable in producing diagnostic ST-segment depression. In patients showing ST-segment depression at rest, it is not necessary to impose any further stress on the patient with the intention of reproducing the anginal pain. The authors' studies and those performed previously by other workers have shown that, in the progression of events leading up to anginal pain, ST-segments become depressed before the onset of pain and often remain depressed long after the pain has disappeared. Of the 23 patients who were evaluated for endarterectomy, ST-segment depression in the electrocardiogram was associated with complete occlusion of at least one major coronary branch in 10 patients; the ST-depression was present at rest in 4 of these, and in 6 it was induced by exercise. These 10 patients and an additional one, in whom atypical history and equivocal results of the electrocardiographic test after exercise prompted the use of coronary angiocardiography as diagnostic method, underwent endarterectomy. Coronary angiography may be useful in locating segments of arterial occlusion.

Having established the diagnosis and then having decided to operate, the authors were faced with the problem of obtaining some sort of semiquantitative baseline from which to evaluate the postoperative results. Exercise on a motor-driven treadmill can be performed during continuous electrocardiographic monitoring. Treadmill testing was useful in demonstrating objective indications of improved coronary perfusion in 4 survivors of coronary endarterectomy who were available for study. Of the 4 patients, the postoperative treadmill tests disclosed no deviations of ST-segments in walks of up to 20 minutes' duration, of 2½ miles per hour speed, in 2 patients who were restored to full activity and were capable of heavy physical exertion. Of the other 2, one had postoperative anginal pain requiring glyceryl trinitrate on rather strenuous effort. While his postoperative tracings showed some variations in the T-wave patterns, there were no changes in ST-segments, and he was able to walk up to 15 minutes on one occasion without pain. Postoperative tests gave mildly positive results during the first 2 months in the 4th patient, though on one occasion he was able to walk 10 minutes without pain. Treadmill testing also was helpful in evaluating the effect of glyceryl trinitrate and procainamide on the anginal syndrome.

The Surgical Treatment of Angina Pectoris. W. P. Longmire Jr., J. A. Cannon and A. A. Kattus. A. M. A. Arch. Int. Med. 104:886-892 (Dec.) 1959 [Chicago].

Current surgical attempts to improve myocardial circulations in patients with angina pectoris have been directed along 2 lines: (1) attempting to increase the intramural coronary anastomosis, and thereby provide more efficient and effective utilization of arterial blood available to the heart, and (2) increasing arterial flow, both into the coronary arterial system and into available intramural collateral channels. After extensive studies on autopsy specimens and dissection of the coronary arteries of dogs, a suitable technique and special instruments were devised by one of the authors for reestablishing blood flow through the obstructed main coronary arteries and their major branches by removal of the thickened atheromatous intima (direct-vision endarterectomy). This procedure was carried out in 10 patients, between the ages of 38 and 63 years, with incapacitating angina pectoris. Nine of the 10 patients were considered to have angina decubitus. Four patients were considered to have a normal electrocardiogram at rest; in the other 6 patients the electrocardiographic tracing made at rest showed abnormalities compatible with myocardial ischemia or questionable infarction. Typical temporary ST-segment depression and depression of the T wave occurred with exercise on the treadmill in 7 patients.

In all of the 10 patients operated on, the extensive coronary atherosclerosis observed at surgical intervention substantiated the preoperative diagnosis of severe incapacitating angina pectoris. Disease of the major coronary arteries with patent distal vessels was found in each patient, and theoretically total coronary blood flow could have been increased by the proposed operation. Five patients have survived the endarterectomy, one for 1 year and 3 months. All have been improved, as judged by their clinical course and by evaluation of the treadmill exercise test.

Emergency Mitral Valvular Commissurotomy Preceding a Second Aortic Embolectomy. E. S. Hurwitt, P. Glotzer and J. B. Schwedel. A. M. A. Arch. Surg. 79:1009-1012 (Dec.) 1959 [Chicago].

The authors report on a 53-year-old woman on whom emergency mitral valvular commissurotomy was performed at the Montefiore Hospital in New York. The patient was admitted to the hospital with the chief complaint of progressive dyspnea of 2 weeks' duration. She had an attack of acute rheumatic fever 21 years previously. For the past 18 years she had noted progressive dyspnea on exertion. On admission, the patient was considered to be in mild congestive failure, with an uncontrolled atrial fibrillation, and she was given a digitalis preparation. On the morning of her third hospital day she suddenly showed the classical signs of embolization to the bifurcation of the abdominal aorta. Embolectomy was performed with the aid of spinal anesthesia within 4 hours of the embolization. A large clot was removed from the bifurcation of the aorta and from both iliac arteries, with prompt restoration of the pulses in both legs. Anticoagulant therapy was instituted with heparin and continued with warfarin; the patient was ambulatory on the 5th postoperative day. On the 7th postoperative day the patient again showed the clinical picture of embolization to the aortic bifurcation. Phytonadione (vitamin K_1) oxide was given intravenously, and within 4 hours of the onset of this acute episode, a mitral valvular commissurotomy was accomplished, with the aid of general anesthesia, through the left auricular appendage. There was a tight mitral stenosis, with no insufficiency, and no thrombi were felt; a satisfactory opening of the valve was accomplished. After closure of the chest, the previous laparotomy incision was opened, and a large, completely obstructing embolus was removed through the previous aortotomy incision. The total operating time for the 2 procedures was 2 hours and 20 minutes.

After a complicated postoperative course, the patient was discharged from the hospital after a 7 weeks' stay. She has continued to be well to date, with no evidence of circulatory insufficiency to her legs or neurological deficit and with profound relief of her complaints at the time of her admission. This is the case of the second known patient to survive 2 aortic embolectomies, and of the third reported patient with aortic embolization who was treated with combined commissurotomy and embolectomy. Emergency mitral commissurotomy preceding aortic embolectomy in patients with mitral stenosis merits favorable consideration.

Pulmonary Nocardiosis: Case. M. M. Brea, G. P. Ansaldo and C. M. Brea. Rev. Asoc. méd. argent. 73:441-444 (Nov.) 1959 (In Spanish) [Buenos Aires].

Pulmonary nocardiosis causes severe pulmonary lesions, becomes systemic with formation of multiple abscesses, and causes rapid emaciation and death, unless early treatment with sulfadiazine is established. The early symptoms of the acute form are those of pneumonia, with suppuration and cavitation of the lung tissue, empyema, early enlargement of the regional lymph nodes, and formation of abscesses on the ribs. Pulmonary tuberculosis is the most frequent complication. Splenomegaly and hepatomegaly appear in the late stages of the disease. The disease should be suspected in the presence of symptoms of acute or subacute pulmonary infection which do not subside on the administration of antibiotics, the only exception being sulfadiazine to which pulmonary nocardiosis always responds. A diagnosis is made by identification of Nocardia asteroides in the material obtained from the lesion as well as from the sputum. The diagnosis should be confirmed by cultures with special mediums. Pulmonary nocardiosis was always fatal before the appearance of antibiotics. The treatment consists of drainage of the pleural empyema and the parietal abscesses and of the administration of sulfadiazine in daily doses which range between 6 and 7 Gm. for as long as 5 or 6 months.

A man, 56 years old, requested treatment for mild pulmonary symptoms of 6 months' duration. He had lost weight, and an abscess had developed on the ribs. A roentgenogram of the chest showed an extensive infiltrating lesion of the upper lobe of the lung. A diagnosis of nocardiosis was made on the positive results of microscopic examination of pus from the abscess and by cultures of the same material. The treatment consisted of surgical removal and drainage of the abscess and the administration of sulfadiazine in daily doses of 7 mg. for 5 consecutive months. The roentgenogram of the chest, after completion of the treatment, showed healing of the pulmonary lesion, with transformation of tissue into a zone of fibrosis.

Bacterial Endocarditis After Mitral Commissurotomy: Report of Four Cases. Y. Bouvrain, R. Slama and J. N. Mercier. Arch. mal. coeur 52:1227-1237 (Nov.) 1959 (In French) [Paris].

The authors report on 2 men and 2 women, between the ages of 29 and 39 years, who underwent mitral commissurotomy and in whom subacute bacterial endocarditis followed the surgical intervention. In the first patient, Staphylococcus pyogenes var. albus was determined by blood culture as the pathogenic agent. In the second patient Pseudomonas aeruginosa (pyocyanic) was found on culture of the blood, and in the third patient Staph. pyogenes var. aureus was found. More than 20 bacteriological cultures of the blood of the fourth patient remained negative. The marked increase in the size of the spleen and the fact that antibiotic treatment with streptomycin and penicillin, and, in addition, prednisolone therapy, restored the temperature to normal were thought to be sufficiently significant for considering the presence of subacute bacterial endocarditis with negative blood cultures.

The onset of the condition occurs within less than one month after the surgical intervention. In most of the cases a staphylococcus is the pathogenic agent; this may be due to the systematic employment of penicillin combined with streptomycin for postoperative prophylaxis. The clinical picture is remarkable for the absence of the fundamental classic symptoms, such as petechiae and clubbed fingers. Subacute bacterial endocarditis follows more frequently surgical intervention on the aortic valve than a mitral commissurotomy. Its prognosis is unfavorable. Of the small number of 38 patients whose cases were collected from the literature, 20 died, and 2 of the 4 patients in the authors' series died, a mortality rate of about 50%.

Chronic Idiopathic Pericardial Effusion Without Tamponade. D. C. Connolly, T. J. Dry, C. A. Good and others. Circulation 20:1095-1105 (Dec.) 1959 [New York].

Persistent pericardial effusion in the absence of obvious preceding or concurrent disease presents a baffling problem. In such cases chylopericardium, cholesterol pericarditis, lupus erythematosus, malignant disease, myxedema, severe anemia, and scleroderma must be considered. The authors present the histories of 6 patients who had chronic pericardial effusion, without cardiac tamponade. All 6 patients were women, and 5 were menopausal. There was no evidence of active tuberculosis or rheumatic disease at the time of examination, and none had myxedema or signs of systemic lupus erythematosus. Evidence of cardiac tamponade was not present in any of these patients, but the venous pressure was grossly increased in one because of superior vena caval obstruction some 25 years previously. The duration of the pericardial effusion ranged from 1 to 11 years; fluid may have been present as long as 29 years in one of the patients. In another patient the chronicity of the effusion was assumed from the roentgenologic findings of cardiac enlargement 2 years before. In a third case the pericardial effusion was possibly present for only a short period.

None of the 6 patients gave a history suggesting an episode of acute pericarditis. Examination of the pericardial fluid or tissue gave no clue to the etiological factor. One case is of interest in view of the coincidence of pericardial effusion and polycythemia, which almost certainly was induced by ingestion of a cobalt-containing preparation of iron. In this patient disappearance of the effusion followed correction of the polycythemia.

In 5 patients the pericardial fluid measured from 700 to 1,200 ml. at the time of operation. The operation on 4 patients consisted in the creation of a "pleuropericardial window," which previously had been found satisfactory in patients with pericardial effusion. Follow-up for variable periods has not revealed any evidence of recurrence of pericardial effusion in these 6 patients, all of whom noted subjective improvement. The importance of angiocardiography as an aid to the diagnosis of pericardial effusion again is emphasized.

Primary Lymphosarcoma of the Lung. E. R. Hall Jr. and B. Blades. Dis. Chest 36:571-578 (Dec.) 1959 [Chicago].

The authors report on a 61-year-old man and 2 women, aged 49 and 70 years, with primary lymphosarcoma of the lung, who were operated on at the George Washington University Hospital in Washington, D. C. In the man, thoracotomy revealed that the middle lobe was completely atelectatic. There were nodular infiltrations throughout the middle lobe and the superior portion of the lower lobe. Neoplastic tissue engulfed the pulmonary artery and the main bronchus. The lesions were considered inoperable. On the 5th day after the thoracotomy, irradiation therapy was administered to the anterior and the posterior chest on the left. The patient was discharged from the hospital, but was readmitted 5 months later when a general bone survey by roentgenogram revealed metastatic lesions involving the skull, spine, and left 5th rib. The patient died 10 months after the thoracotomy.

The younger woman was subjected to a right-sided pneumonectomy because of a 6-cm. mass in the right lower lobe extending across the oblique fissure into the right middle lobe; there was no evidence of enlarged hilar nodes. Seven years after the surgical intervention, there was no evidence of recurrence or metastasis in this patient. Thoracotomy performed on the older woman revealed a 4-by-5-cm. triangular area in the left upper lobe, which appeared red and atelectatic. Extending from this area toward the hilus was an irregular, hard tumor invading the mediastinal structures. The pulmonary artery and the superior vena cava were surrounded by the tumor. The lesions were considered inoperable. Two weeks later irradiation therapy was started, and the patient was also treated with nitrogen mustard and triethylene thiophosphoramide for palliation. The patient died 2 years after the thoracotomy.

From this small series, one would believe that the prognosis in patients with resectable pulmonary lymphosarcoma is more promising than in those with bronchiogenic carcinoma. The extent of resection must depend on the location of the lesion and the age of the patient. There are varying views on the use of irradiation therapy. Some workers feel it should always be employed, regardless of the extent of the lesion or the thoroughness of the operation, while other workers use it only for recurring lesions.

Hemorrhage from Esophageal and Gastric Varices. L. Leger, P. Dêtrie and P. Guyet. Arch. mal. app. digest. 48:1304-1332 (Nov.) 1959 (In French) [Paris].

The origin of hemorrhages in portal hypertension is far from being established. Gastric hemorrhage occurs frequently as an isolated accident which endangers the patient's life and may require an emergency hemostasis. Although vasomotor disorders and disturbances in the blood constitution play a role, the reality of hemorrhages from ulcerations of esophageal varices is undeniable, whatever the mechanism may be. The esophageal varices often reach beyond the greater curvature of the stomach where the source of bleeding may be situated. Associated lesions, especially the ulcerative, are also responsible. The controversial point is the frequency of any particular mechanism. The role of varicose ulceration in gastric hemorrhage is dominant, although not exclusive.

Twelve cases of hemorrhage from esophageal varices associated with different lesions are reported and analyzed from the clinical and therapeutic points of view. Therapeutic emergency measures include the application of a double-balloon gastroesophageal tube, blood transfusion, drip feeding, and vitamin therapy for a period of time compatible with the patient's respiratory condition. Failure of the tamponade or recurrence of the bleeding is indication for surgical treatment. Ligation of esophageal varices is often a first emergency step before portacaval anastomosis. The surgical approach varies. The transthoracic approach is technically the most convenient, as it gives a desirable visualization of the stomach's greater curvature. It is contraindicated in patients who are exhausted or not well prepared for the operation. The abdominal approach permits an easy lowering of the esophagus after resection of the xiphoid process.

Once the esophagus is reached, a longitudinal incision should reach the entire thickness of the wall.

It may be advisable to add a double vagotomy and a gastroenterostomy to the ligation of the esophageal varices, as a means of reducing the gastric acidity and its effect on the esophagus. It is preferable to operate early after a short attempt of tamponade with balloon, the time interval being used to transfuse and prepare the patient. Once the operation has been undertaken, the surgeon should not hesitate to continue the investigation and to secure the indispensable visualization until the hemorrhagic focus is found. These procedures represent a possibility of improving the prognosis in portal hypertension with gastroesophageal hemorrhage.

The After-Effects of Removal of a Ruptured Spleen.

H. Begemann and W. Gehle. German M. Month. 4:378-384 (Nov.) 1959 (In English) [Stuttgart, Germany].

The authors report on 310 previously healthy persons who underwent splenectomy for traumatic rupture of the spleen. Seventy of these patients died in the postoperative period. Of the 240 survivors, 209 (170 male and 39 female patients), between the ages of 4 and 67 years, were subjected to follow-up examinations, mostly in their own homes in Freiburg im Breisgau, Germany, within 6 months to 36 years after the splenectomy, and, on the average, within 8 years and 9 months postoperatively. Postoperative infections of the lung and pleura were more common among these patients than among those who had undergone other upper abdominal operations, but the incidence of all types of infections years after the splenectomy was not higher among these patients than among the general population. Disturbances of growth and development were not observed in patients who at the time of the splenectomy were still children. Functional disorders of the autonomic nervous system were frequently manifested by gastric and cardiac symptoms and by a general reduction of physical capacity. A striking symptom in many patients was intolerance to alcohol. This intolerance was manifested by nausea, vomiting, and, in some patients, abdominal pain, and it was often the only after-effect of the splenectomy or, at least, the only significant one. Apart from an increase in siderocytes and Howell's bodies, the only moderately constant change in the blood picture was a lymphocytosis. The hemoglobin concentration and the red blood cell count returned to normal in 5 to 8 months.

These observations suggest that splenectomy has little effect on most healthy persons, but in a few it may lead to troublesome syndromes or an increased susceptibility to infections; this may be due to a failure of other organs to take over the functions of the spleen. It is difficult to lay down any general principles for the medicolegal assessment of patients after splenectomy.

On the Drying Test of Gallbladder Bile: A New Method for Diagnosis of Gallstones.

H. Miyake. A. M. A. Arch. Surg. 79:1032-1043 (Dec.) 1959 [Chicago].

The author reports on a new method for diagnosis of cholelithiasis, as devised and practiced in the department of surgery of the University Hospital in Fukuoka, Japan, particularly in patients in whom the stones are composed of bile pigment (bilirubin). This type of biliary calculi may be found in a high percentage of Japanese patients with gallbladder disease. To perform the "bile drying test," bile was obtained from the gallbladder by needle aspiration during laparotomy; the aspirated fluid was placed on a glass plate and dried in an incubator at 37 C for 24 hours. Macroscopic examination of the specimen revealed a regular pattern of crystals lined up radically in most cases of cholecystitis with calculi, while no crystals or partial crystallization were observed in cases of cholecystitis without calculi. Microscopic examination of the dried bile specimens revealed various patterns of crystallization; there were typical crystals which showed a fern-like structure or a crystal nucleus; atypical crystals showed a thrum-like, cross, or plate structure. Of 176 patients on whom drying tests were performed, 85 had cholecystitis with calculi, 67 had cholecystitis without stones, and 24 had a normal biliary tract. Of the 85 patients, microscopic examination of dried bile specimens showed typical crystals in 68, atypical crystals in 15, and no crystals in 2. Of the 67 patients, the drying test showed typical crystals in 4, atypical crystals in 19, and negative results were obtained in 44. In the 4 patients with typical crystallization in the dried bile, the operative findings seemed to indicate that calculi might have been present and passed through the biliary tract.

The reported data, obtained by gallbladder puncture during surgical intervention, show that there is a distinct difference in the dried bile pattern of patients with cholecystitis with calculi, those without calculi, and those with a normal biliary tract, even though there are a few exceptions. In an attempt to obtain gallbladder bile (bile "B") before surgical intervention to serve as an aid in diagnosis of gallstones, "B" bile was obtained through a duodenal tube and subjected to the drying test. Results were as follows: Crystallization was rarely observed when the biliary tract was normal. Crystallization was mostly negative or atypical in patients with cholecystitis without calculi. Typical crystals were observed in most patients with cholecystitis with calculi. The special forms of crystallization, as revealed by the drying test, are not directly related to the presence of calculi, but chiefly to the function of the gallbladder or the degree of its inflammation. Since the function of the gallbladder is usually impaired in patients with cholelithiasis, especially in those with "bilirubin stones," who frequently show severe inflammation, the drying test is far more effective as a diagnostic aid in the presence of biliary calculi than any other customary test, particularly in Japan where "bilirubin stones" dominate. If "B" bile can be obtained, this test is the method of choice for the determination of the functional impairment and the degree of inflammation of the gallbladder.

Hirschsprung's Disease in the Newborn. O. Swenson and J. H. Fisher. A. M. A. Arch. Surg. 79:987-993 (Dec.) 1959 [Chicago].

The authors report on 55 newborn infants with congenital megacolon (Hirschsprung's disease), who were observed at the Boston Floating Hospital for Infants and Children. This disease is one of the most frequent causes of acute intestinal obstruction. with symptoms and signs, such as vomiting (present in 27 infants of this series), intractable constipation (present in 40 infants), and abdominal distention (present in 38 infants), which may be indistinguishable from those due to another cause of intestinal obstruction, such as ileal atresia. There are certain conditions, such as meconium plug syndrome or cretinism, which give rise to symptoms of intestinal obstruction, while the roentgenographic findings may be suggestive of Hirschsprung's disease by identifying dilated loops to be colon and thus excluding obstruction of small intestine. A rectal biopsy should be performed to rule out these other conditions. Rectal biopsy is also indicated in certain infants who have the symptoms of Hirschsprung's disease and yet do not have characteristic roentgenographic findings. Barium enema failed to establish the diagnosis in 10 infants, but rectal biopsy established it. Photomicrographs of a rectal biopsy section which show ganglion cells in Auerbach's plexus exclude the diagnosis of Hirschsprung's disease, while a rectal biopsy section containing no ganglion cells establishes this diagnosis.

In most of the newborn infants with Hirschsprung's disease, the aganglionic lesion extends no higher than the sigmoid colon. In these patients a small rectal tube may be passed beyond the aganglionic segment, and the intestinal obstruction relieved by colonic irrigations with small quantities of sodium chloride solution. It is best to treat enteritis, to which infants with Hirschsprung's disease are susceptible, by intravenous feedings, in addition to colonic irrigations similar to those given to relieve the acute intestinal obstruction. An elective colostomy may be done when the infant is several days old, after the diagnosis of Hirschsprung's disease has been substantiated by rectal biopsy. The definite resection of the aganglionic segment and the colostomy may be carried out when the child weighs 25 to 30 lb. (11.3 to 13.6 kg.). A biopsy of the colon wall should be secured at the time of colostomy to be certain that ganglion cells are present in this segment. If the colostomy is placed in an aganglionic segment, it will not function properly.

Mallet Finger. D. Flinchum. J. M. A. Georgia 48:601-603 (Dec.) 1959 [Atlanta].

The term "mallet finger" implies the characteristic droop of the distal phalanx from disruption of the terminal extensor mechanism. The lesion may be caused by a sudden blow against the end of the finger, as from a ball, or else by striking the finger tip against some object or by dorsal laceration over the distal interphalangeal joint. There are 2 main types of injury in mallet fingers. The most common is a frayed break or stretch through the distal portion of the extensor tendon. Occasionally a laceration is noted. The other type of injury is an avulsion fracture of the proximal portion of the dorsal aspect of the distal phalanx, where the insertion of the distal tendon is pulled off with the bone fragment; the tendon is intact. Mallet finger is extremely difficult to treat without some residual cosmetic or functional loss. The finger must be splinted, so as to hold the lateral bands extending through to the distal phalanx relaxed. This is done by holding the proximal interphalangeal joint flexed and the distal interphalangeal joint in extension. It is difficult to hold this relaxation.

Of 25 cases of mallet finger observed during the past 3 years and treated by various methods, only 5 results can be considered normal; 6 conditions are good, 8 are improved, and 1 was not helped. Five patients were not treated. The author believes that the following methods of treatment are desirable. External splinting with a dorsal and palmar padded aluminum splint, holding the proximal interphalangeal joint in flexion and the distal one in extension for 6 weeks, offers the best chance of satisfactory results in younger patients. In older persons, laborers, and those apt to have some joint limitation, a Kirschner wire should be inserted across the distal interphalangeal joint to hold this joint in extended position, and this should be combined with an external aluminum splint to hold the proximal interphalangeal joint flexed. The splint is removed after 3 weeks to allow flexion and extension of the proximal interphalangeal joint. The Kirschner wire can be inserted initially or after 3 weeks of external splinting. This splinting method of treatment should be done early, within the first week of injury, although it can be tried as long as a month after the injury has been sustained. The distal interphalangeal joint should be kept extended for 6 weeks. Some slight residual drooping or hyperextension of the proximal interphalangeal joint will remain in most patients.

Accidental Seeding of Cancer in the Operative Area. J. Sonneland. Northwest Med. 58:1687-1692 (Dec.) 1959 [Seattle].

Some of the failures in cancer surgery are due to accidental seeding of cancer in the operative field. The author presents 5 cases of recurrence in the abdominal incision observed in the Spokane (Wash.) area; 2 of the 5 cases are personal cases. Increased attention should be paid to the local contagion of cancer. Local recurrences may be reduced by preoperative surface sterilization of the tumor where applicable, by scrupulous local quarantine of the cancer, by treatment of the fomites of the operating table with resterilization or with one-half strength Dakin's solution, and by treatment of the operative area with Clorpactin.

Postoperative Nourishment. H. F. Harbitz and Ø. Oyen. Tidsskr. norske laegefor. 79:1219-1222 (Nov. 1) 1959 (In Norwegian) [Oslo].

The ordinary postoperative diet in Aker Hospital, Oslo, for patients undergoing surgery in the gastrointestinal tract has been low in protein and calories. The new postoperative diet adopted furnishes 100 Gm. of protein and consists of 2,000 calories a day, and is given earlier in the postoperative course than the former diet. The increased protein content depends on the addition of dried milk, eggs, and cheese. Nitrogen-balance studies on 17 patients after partial gastrectomy (7 of whom were given the previous diet and 10, the new diet) showed that none of the 7 were in positive protein balance after 13 days, while on the diet rich in protein positive protein balance was attained by 8 of the 10 on the 7th postoperative day and by all 10 after 13 days.

NEUROLOGY & PSYCHIATRY

Diagnosis of Huntington's Chorea. O. S. Dalgaard and K. Noreik. Tidsskr. norske laegefor. 79:1224-1227 (Nov. 1) 1959 (In Norwegian) [Oslo].

The characteristic picture in Huntington's chorea depends on hereditary occurrence of typical choreatic movements in a grown person, progressive in course, with simultaneously developing dementia. Heredity is dominant. Less clear symptoms can give the basis for the diagnosis only when compared with the characteristic transmission. The symptoms may occur as preliminary stages or early symptoms, with later development of the typical picture, and in some atypical cases remain the only or the dominating symptoms; this condition is designated as "chorea sive chorea." Of 14 patients (10 men and 4 women) with Huntington's chorea treated at Gausdal Hospital, in Norway, 8 were admitted with incorrect diagnosis. If there is positive family history and the classical symptoms are present, the diagnosis is assured. If positive family history is lacking but the classical symptoms are present, more intensive family investigation will probably give positive results. If the classical symptoms are absent or not marked but other symptoms are seen and the family history is positive, possible progression of the symptoms may be decisive; if there is no positive family history, renewed intensified investigation of the family may give results. Since at present no curative treatment is known, reduction in the number of Huntington chorea patients can occur only by reduction of the reproductive frequency in bearers of the hereditary tendency.

Vestibular Dysfunction in Childhood Schizophrenia. E. G. Colbert, R. R. Koegler and C. H. Markham. A. M. A. Arch. Gen. Psychiat. 1:600-617 (Dec.) 1959 [Chicago].

Hyporeactivity and paradoxical vestibular reactions have been reported in adults with schizophrenia. There is also a good deal of presumptive evidence that children with schizophrenia have some problems in the area of vestibular functioning. Since, moreover, there continues to be doubt about schizophrenia occurring before adolescence, the authors felt that it would be important to find whether there are common physiological denominators among adult schizophrenics and so-called childhood schizophrenics. Tests of vestibular and optokinetic function were performed on 43 children with schizophrenia, 18 with behavior problems, and 32 normal children. The normal and behavior-problem children had reactions similar to those of normal adults. The majority of schizophrenic children had markedly depressed or absent vestibular responses to caloric and rotational tests. The degree of hypoactivity was more marked in the younger children with schizophrenia. The responses of some schizophrenic children varied from one observation period to the next, unlike the responses of the controls and of normal adults. There were fewer and less severe manifestations of vertigo than were seen in the controls. This study suggests the possible existence of a neurophysiological continuum between a type of childhood schizophrenia and a type of adult schizophrenia.

Long Survival in Medulloblastoma: Three Cases. A. Lima, L. Antunes and C. Marçal. Rev. españ. oto-neuro.-oftal. 18:233-237 (July-Aug.) 1959 (In Portuguese) [Valencia, Spain].

Medulloblastomas are highly malignant and rapidly fatal if they are not surgically removed; yet the average survival period after removal does not exceed 1½ years. During the years from 1943 to 1958, however, 42 patients with medulloblastomas were observed in the Instituto de Neurologia of the Faculty of Medicine of Lisbon University, and 3 of these patients lived for more than 4 years after the operation; they included 2 adults (a man and a woman) and a child, 7 years old. The 3 patients were seen for the first time from 4 to 8 months after the appearance of severe neurological symptoms. The tumor was located in the cerebellar fossa and in the left cerebellar hemisphere, respectively, in the 2 adults; in the child it was located in the vermis cerebelli. The treatment consisted of surgical removal of the tumor, followed by roentgenotherapy. The immediate and late postoperative periods were uneventful.

The patients lived from 4 to 4½ years in good health, but by the end of this period severe neurological symptoms reappeared in the 2 adults. The man was subjected to a cervical laminectomy; a tumor was encountered, but further operation was interdicted. Autopsy revealed that the spinal leptomeninges were involved by a tumor, from the lower bulbar region to the cauda equina, which differed histologically from the one previously removed from the cerebellar fossa. The woman underwent a second operation for a recurrent medulloblastoma. Today this patient is free from neurological symptoms, but she is still under roentgenotherapy. The child is well 4 years after the first and only operation, which was followed by roentgenotherapy up to a total dosage of 27,000 r. Histologically the tumor removed from the vermis cerebelli consisted of neuroblasts and adult nerve cells. The authors believe that the rare cases of long postoperative survival in patients with medulloblastomas are due to the structure of the tumors which consist mainly or purely of either glial or nerve cells.

Inferior Nasal Quadrantanopsia in Pseudotumor Cerebri. J Dersh and N. S. Schlezinger. A. M. A. Arch. Neurol. 1:695-699 (Dec.) 1959 [Chicago].

Occasionally the ophthalmologist or the neurologist is confronted with a patient with bilateral papilledema associated with increased intracranial pressure, for which no cause can be found, even after extensive neurological examination and neurosurgical intervention. The signs and symptoms indicative of increased intracranial pressure simulate those of a cerebral tumor, and, therefore, the term "pseudotumor cerebri" has been applied to this condition. Some patients with the clinical features of pseudotumor cerebri exhibit a visual field defect in the form of a unilateral inferior nasal quadrantanopsia. Three such cases were observed for periods varying from 5 to 13 years at the Wills Eye Hospital, Philadelphia. It was noted in these cases that the inferior nasal quadrant defect remains essentially unchanged, without progression, and that it is not a threat to vision, provided that the original condition has been completely resolved.

Emphasis is placed upon the need to recognize the inferior nasal quadrantanopsia as a sector type of visual field defect which, in the presence of increased intracranial pressure, has no localizing significance and does not warrant exploratory neurosurgical intervention. Of several possible explanations considered, the one preferred is the concept of a gliosis of the optic nerve, commencing in the glial sheath of the nerve head on the temporal side.

A Restricted Form of Cerebellar Cortical Degeneration Occurring in Alcoholic Patients. M. Victor, R. D. Adams and E. L. Mancall. A. M. A. Arch. Neurol. 1:579-688 (Dec.) 1959 [Chicago].

The authors report observations on 50 alcoholic patients (46 men and 4 women) who presented a cerebellar syndrome. The most prominent abnormality was an ataxia of stance and gait and of the individual movements of the legs. The arms were relatively little affected, and nystagmus and dysarthria were usually absent. Instability of the trunk was common. The patients could be divided into 3 categories. In the first group, which comprised half of the patients, the disease evolved over a period of several weeks or months, after which it remained unchanged for many years. In the second group, the disease evolved over a period of several years, but in some of these patients the clinical condition eventually stabilized. In the third and smallest group, mild stationary signs of cerebellar disease had been present for several years; on this background there occurred a worsening of the cerebellar signs, but these, in turn, were again stabilized.

The essential pathological change, as observed in 11 autopsied cases, was a degeneration of all the neurocellular elements of the cerebellar cortex, particularly of the Purkinje cells, the changes being restricted to the anterior and superior aspects of the vermis and the hemispheres. The pathological changes were largely confined to that portion of the cerebellum which lies anterior to the primary fissure. The relation between the clinical and pathological findings is meaningful in the light of recent concepts concerning somatotopic localization in the cerebellum. The parts consistently involved in the pathological process, namely, the central lobule and the anterior folia of the anterior lobe, correspond to the "leg area" in the experimental animal; this is in keeping with the fact that ataxia of gait and incoordination of the legs are the most prominent clinical features.

Many etiological factors were considered, but only 2 seemed of importance—alcohol and malnutrition. Although the abuse of alcohol was a feature common to all the patients, 6 had actually been abstinent for varying periods of time before the onset of their disease. Fully 75% of the patients suffered from undernutrition when they were first seen. Malnutrition may also have been a factor in the remaining patients who came under observation years after the onset of their illness, after a period of abstinence from alcohol and improvement in their eating habits.

An extensive review of the literature (235 bibliographical references) disclosed 120 pathologically verified cases in which the disease process was limited to, or was predominant in, the cerebellar cortex. From this group it has been possible to derive the following subdivisions, each with distinctive clinical and pathological features: 1. Sporadic cases beginning in adult life, on a background of prolonged alcoholism, characterized clinically by a chronic course, usually with long periods of stability, and pathologically by predominance of degenerative changes in the anterior superior vermis and hemispheres. 2. Sporadic cases occurring in adult life, associated with carcinoma, characterized clinically by a subacute, steadily progressive course, and pathologically by diffuse and approximately equal degenerative changes in all portions of the cerebellar cortex. 3. Sporadic cases beginning in infancy and childhood, usually progressive and associated with mental retardation, characterized pathologically by diffuse changes in the cerebellar cortex, generally of greater severity in the hemispheres, and by lesions in other parts of the central nervous system. 4. Heredofamilial cases of cortical cerebellar degeneration. 5. Cases characterized pathologically by a selective degeneration of the granule-cell layer, and clinically by an onset in infancy or childhood and by mental retardation. 6. Miscellaneous cases. Considering the frequency with which this syndrome has been encountered on a background of alcoholism, and the stereotypy of the pathological and clinical picture, particularly in regard to the long periods of stability, the authors conclude that the restricted form of cortical cerebellar degeneration seen in alcoholics represents a clinicopathological entity.

Acetazolamide in the Treatment of Epilepsy. P. V. Arruda and C. S. Fonseca. Rev. Hosp. clín. 14:365-370 (Sept.-Oct.) 1959 (In Portuguese) [São Paulo, Brazil].

Sixty-two patients with an epileptic condition of at least 2 years' duration, who had been previously treated with different anticonvulsive drugs for more than a year without obtaining satisfactory results, were treated with acetazolamide in addition to the usual medication for epilepsy. There were 3 age groups. Seventeen patients were between 4 and 12 years; 12 were between 13 and 18 years; and 33 were between 19 and 48 years. Twenty-three patients were psychotic. The daily dose of acetazolamide was 375 mg. in 53 patients, 250 mg. in 4, 500 mg. in another 4, and 125 mg. in 1. The treatment lasted for 3 to 20 months, each patient being examined every 10 days at the beginning, then every month. As the results of the combined therapy became satisfactory, the doses of the usual anticonvulsive drugs were decreased. Acetazolamide became the only therapy in 6 patients.

The convulsive attacks were completely controlled under the treatment in 25 patients, including 8 of the 17 children in the 4-to-12-year age group. This control was obtained at the end of 3 to 5 months in 5 patients, 8 to 10 months in 4 patients, 11 to 15 months in 5 patients, and 16 to 20 months in another 5. The frequency and intensity of the attacks decreased in 20 patients, including 6 under 12 years of age, after a period of 8 to 20 months. The acetazolamide therapy had no effect on 11 patients, and in 6 the clinical picture became worse. There was improvement of the mental disorder in 8 of the psychotic patients, and no change in 13, although in 9 of these the convulsive attacks had been completely controlled. The psychic condition became worse in 2 patients. Electroencephalographic data were consistent with the clinical results, and in 12 of the patients whose attacks were controlled, the electroencephalogram became normal. The treatment was well tolerated. The findings indicate that, if the acetazolamide therapy is not effective during the first week, it should be discontinued.

GYNECOLOGY & OBSTETRICS

Emergency Arterenol Therapy in Obstetrics. J. C. G. Machado. Rev. brasil. med. 16:699-706 (Oct.) 1959 (In Portuguese) [Rio de Janeiro].

Arterenol was given as a vasoconstrictor to 32 patients admitted to the obstetric service of the Rocha Faria Hospital in Rio de Janeiro. The patients required emergency treatment for shock or an insufficient circulation caused by different conditions, such as uterine hemorrhage, rupture, abortion, placenta accreta, and retained placenta. The dose of arterenol varied from 2 to 15 cc., and the mode of administration was either intramuscular injection or intravenous perfusion in a dextrose solution. The therapy was successful in reversing the state of shock and in raising the blood pressure and maintaining a satisfactory level in 26 patients. Arterenol failed in 3 of 6 ectopic pregnancies, in 1 of 3 uterine ruptures, in 1 of 5 abortions, and in 1 of 2 placentae accretae. The intramuscular administration was effective in patients with recent venous collapse, in whom it was possible to refill the peripheral vessels and recanalize the veins. The intravenous perfusion was successful in raising and controlling the arterial pressure. Once the desired level was reached, the drip perfusion was slowed down. The average dose in perfusion was 4 ampuls of 1 cc. each in a dextrose solution. Arterenol is also effective in traction on nerve plexuses, especially if shock is recent. It is ineffective when the loss of blood is too great and/or when it is complicated by toxic hepatitis or lower nephron syndrome.

Hyperthyroidism in Pregnancy: Treating Hyperthyroidism During Pregnancy Without Impairing Fetal Thyroid. J. H. Holt. J. Kansas M. Soc. **60**:537-539 (Dec.) 1959 [Topeka].

Fetal loss and abnormalities have been reported when antithyroid drugs were used throughout pregnancy, and both uncontrolled hyperthyroidism and uncontrolled hypothyroidism were reported to be accompanied by a high incidence of fetal anomalies and monstrosities. Therapy of the pregnant woman with hyperthyroidism must be different from that of the nonpregnant woman, because the following substances are known to cross the placental barrier: iodine, radioiodine (I^{131}), antithyroid drugs of the thiourea type, and desiccated thyroid, and it is important that the normal physiology of the fetal thyroid not be interfered with.

The author presents the histories of 5 pregnant women with hyperthyroidism. Three of these were treated by antithyroid drugs (thiocarbamides) followed by a subtotal thyroidectomy. Hypothyroidism was carefully avoided during the preoperative medication. There were neither late complications of pregnancy nor fetal abnormalities. The fourth woman was 5½ months pregnant when she was found to have primary hyperparathyroidism. The recommendation that she undergo thyroidectomy after preparation with antithyroid drugs was refused, and the antithyroid preparation prescribed was taken irregularly and was discontinued during the last month of pregnancy; she gave birth to a microcephalic male infant. The case of the fifth woman with a nontoxic diffuse goiter associated with pregnancy was included in this series only to emphasize conservative management of thyroid disease during the last trimester of pregnancy. This patient was 8 months pregnant when she was found to have a nontoxic diffuse goiter. She gave birth to a normal girl, and a few days after delivery she was subjected to a thyroidectomy. The author concludes that careful preparation with the thiourea derivatives followed by surgery is a safe method for the management of hyperthyroidism during the first 2 trimesters of pregnancy.

Home on the Second Day: The Bradford Experiment: The Combined Maternity Scheme. G. W. Theobald. Brit. M. J. **2**:1364-1367 (Dec. 19) 1959 [London].

The most important period for detection of hypertension in pregnancy, for delaying its onset, and for preventing it from becoming an irreversible process; associated with proteinuria, is the period between the 24th and 34th weeks. In order that more beds might be available for the antenatal care of all primigravidas and of the multigravidas who had shown abnormalities in previous pregnancies, the staff of St. Luke's Maternity Hospital in Bradford, England, decided to decrease the number of lying-in beds. This was done by discharging a certain number of patients on the second day of puerperium. The rules established by the hospital for this early discharge were that the baby should be healthy and weigh at least 6½ lb. (2,948 Gm.), that the mother should be fit to move, and that the home conditions should be suitable. The domiciliary midwives inspect all homes before the patients are discharged, and the patients' physicians are informed.

During the first full year of operation of this program, 2,898 women were delivered of 2,969 babies; 741 (26%) were sent home within 48 hours after the delivery, to the care of their own physicians and to be visited by the domiciliary midwives. Only 3 of these mothers were rehospitalized, 2 because of secondary postpartum hemorrhage, and 1 because of fever. The combined maternity scheme, agreed upon by the hospital staff, the local health authorities, and general practitioners, has resulted in a better antenatal care program. Severe pregnancy toxemia has been almost eliminated from the city of Bradford. The method is not dangerous; it prevents the infant from becoming a culture medium for hospital staphylococci; and it may set a pattern in obstetrics and pediatrics.

Hormonal Mastopathy: A Clinical Study And Outline of Treatment. K. Cuningham and E. H. Wyse. M. J. Australia **2**:711-713 (Nov. 14) 1959 [Sydney].

The authors report clinical observations on 536 patients with hormonal mastopathy, who received treatment at the breast clinic of the Rachel Forster Hospital in Sydney. The patients, who were followed up for 8 years, were mostly in the premenopausal age group. In 75% of the patients, in whom pain, tenderness, swelling, and nodular areas, fluctuating in size, were present in the breast, the symptoms were relieved by the onset of menstruation. A quiescent period of 14 to 18 days ensued, but from the 18th day of the cycle onwards, discomfort increased, preexisting lumps became larger, and the whole breast became swollen until the onset of the next menstrual period. This led the authors to believe that hormonal mastopathy is due to an imbalance between estrogen and progesterone. Fibroadenoma was present in 32 patients; fibroadenosis, in 34; fibrocystic disease, in 189; hormonal mastopathy, in 249; mastopathy due to definite injury, in 10; and carcinoma supervening on hormonal mastopathy, in 22. Fibroadenosis was more common in patients under the age of 40, and the 32 patients with fibroadenoma were under 30. The majority of the patients with fibrocystic disease, however, were over 40. This suggests that, if the hormonal imbalance is of shorter duration, fibroadenosis occurs, but if it is prolonged over the age of 40, a fibrocystic condition will develop.

Treatment consisted of support to the breast, reassurance, administration of vitamin B_1 and luteal hormone, biopsy of all suspicious or persistent masses, and careful and continuous follow-up over a period of months or years. Surgical intervention was performed on 281 patients, 187 of whom had fibrocystic hyperplasia. To date, 249 patients with hormonal mastopathy have not been treated surgically. The high incidence of carcinoma (4.4%) supervening on hormonal mastopathy is significant, inasmuch as all 22 cases occurred in the premenopausal and menopausal age groups, in which the incidence of carcinoma is usually lower than in the age group of 50 or over. It is, therefore, suggested that hormonal mastopathy should be treated early and vigorously, and a careful follow-up, extending over a period of years, should be instituted.

PEDIATRICS

Neonatal Meningitis. E. K. Turner. M. J. Australia 2:806-808 (Nov. 28) 1959 [Sydney].

The author reports an unusual case of neonatal meningitis. The mother of the infant was said to have sinusitis, with a clear nasal discharge throughout pregnancy. At 8 weeks' gestation she developed a yellowish, nonspecific vaginal discharge, which had disappeared at term; at 36 weeks' gestation she developed rubella. A small hemorrhage of dark blood developed 22 hours before delivery, and occasional "spotting" continued until delivery. The mother seemed well, and the female infant looked normal at birth.

Jaundice appeared in the infant at the age of 14 hours, and it remained the predominant symptom. At first a diagnosis of fetal erythroblastosis was entertained, because of an ABO incompatibility between the blood groups of the mother and the newborn infant. The infant then showed gradual decreased action. Her blood group was B_3. Rh positive, and at 40 hours of age she had deep jaundice, the serum bilirubin content being 18 mg. per 100 cc. She resented movement and showed increased "startle" response if disturbed. Her cry was shrill; she was sucking poorly; and the fontanel felt woody. The lumbar puncture revealed a turbid cerebrospinal fluid, 6 ml. being removed; this fluid contained 7,300 polymorphonuclear leukocytes per cubic millimeter. On culture, a streptococcus, group B, weakly hemolytic, was grown. This streptococcus was identical with the one which had been cultivated from the mother's postpartum cervical swab and which was probably a normal inhabitant of her vagina.

When the infant was 41 hours old, treatment was instituted with chloramphenicol, given intravenously in doses of 100 mg. per kilogram of body weight; 1 million units of crystalline penicillin was given intravenously every third hour, and sulfadiazine was administered intramuscularly in a dose of 0.1 Gm. per kilogram of body weight. The infant died at the age of 63 hours. The autopsy confirmed the diagnosis of purulent meningitis, attributed to weakly hemolytic streptococci, group B. Infection had evidently been acquired during the infant's passage through the birth canal, although no perinatal trauma was present. The author also reviewed the case histories of 45 infants with neonatal meningitis in 2 hospitals in Melbourne. Twenty-eight of the infants died. The prognosis of neonatal meningitis is grave, despite early diagnosis and adequate therapy.

Needle Biopsy of the Liver: An Aid in the Differential Diagnosis of Prolonged Jaundice in Infancy. R. Kaye, C. E. Koop, B. M. Wagner and others. A. M. A. J. Dis. Child. 98:699-709 (Dec.) 1959 [Chicago].

The authors performed needle biopsy of the liver in 25 infants, between the ages of 3 weeks and 18 months, with prolonged jaundice, in whom hemoglobin concentration and prothrombin, bleeding, and coagulation times were found to be relatively normal. The jaundice was secondary to biliary atresia in 14 of the 25 infants; it was secondary to hepatitis in the remaining 11 infants. Accurate histological diagnosis for the purpose of differentiating biliary atresia from hepatitis requires samples of liver tissue which include portal as well as hepatic parenchymal cell areas. In biliary atresia the important findings are marked increase in fibrous tissue in the periportal areas, proliferation of bile ducts, intraductal biliary stasis, and maintenance of liver cord pattern. A histological diagnosis of hepatitis is made on the findings of distortion of the lobular architecture by swollen parenchymal cells, many of which are multinucleated giant cells, and of minimal or absent bile duct proliferation and fibrosis in the portal areas. All specimens obtained by needle biopsy will not yield material adequate for diagnostic purposes. In general, specimens of 6 mm. or more in length will prove to be suitable. According to the criteria described, 12 of the 14 biopsies obtained from the infants with biliary atresia and 6 of the 11 biopsies obtained from patients with hepatitis were adequate for diagnosis.

In 5 of the 14 patients with proved atresia of the bile ducts, the correct diagnosis was made on the basis of the biopsy specimen when certain clinical and laboratory findings were more suggestive of hepatitis. The actual or potential value of needle biopsy in avoiding unnecessary laparotomy has been described in 3 infants, in whom diagnostic biopsy specimens were obtained, and operation was withheld. Two of these patients are now clinically well, and the third is doing fairly well. The presence of small amounts of urobilinogen was noted in the urine of all 3 of these patients and in the stool of one of them; small amounts of urobilinogen, however, were seen also in 3 of the 5 patients with biliary atresia and in others reported in the literature. Although a presumptive diagnosis of the disease was made in each of the 3 patients with hepatitis, anatomic confirmation obtained by needle biopsy firmly established the basis for deferring exploratory laparotomy. Needle biopsy, by permitting early definitive diagnosis, may be an aid in avoiding the development of biliary cirrhosis in patients with types of biliary atresia amenable to surgical correction.

Inhalation of Excess Liquor as a Factor in the Production of Hyaline Membrane Atelectasis. K. Campbell. M. J. Australia 2:797-800 (Nov. 28) 1959 [Sydney].

The author has observed that the following conditions are usually associated with hyaline membrane atelectasis: inhalation of excess amniotic liquor, prematurity, typical "grunting" type of respiration, generalized edema and cyanosis, and a self-limited course. A combination of accidental hemorrhage, placenta praevia, and cesarean section is referred to as the excess liquor factor. The maximum incidence of hyaline membrane atelectasis has seemed to be in the group weighing 1,250 to 1,500 Gm. (2 lb. 12 oz. to 3 lb. 5 oz.). Death from hyaline membrane atelectasis takes place almost always before the 48th hour of life.

To test the theory that the inhalation of excess liquor is an essential factor in the production of hyaline membrane atelectasis, the author examined the hospital records of all infants weighing 750 Gm. (1 lb. 10.5 oz.) and more, born from 1955 through 1958, who lived from 1½ to just under 48 hours. There were 135 infants whose alveoli contained, and 223 infants (control series) whose alveoli did not contain, hyaline material. The cases were divided into 7 groups with birth weights of 750 to 999 Gm., 1,000 to 1,249 Gm., 1,250 to 1,499 Gm., 1,500 to 1,749 Gm., 1,750 to 1,999 Gm., 2,000 to 2,499 Gm., and 2,500 Gm. and over. The incidence of the excess liquor factor in the hyaline membrane atelectasis series was proportionally more than double that in the control series. In all groups except the 1,250-to-1,500-Gm. group, the incidence of the excess liquor factor was higher in the hyaline membrane atelectasis series than it was in the controls. This preponderance increases with each increase in weight.

In the 1,250-to-1,500-Gm. group, which is the largest and the most vulnerable, the incidence of the excess liquor factor was less in the hyaline membrane atelectasis series than it was in the controls. This suggests that in this group some special factor is operating. It is at the period of gestation from 30 to 32 weeks that there is clinically the greatest amount of liquor present relative to the size of the fetus. Under such circumstances there would always be a larger amount of liquor present at birth than usual, so that the excess liquor factor would be present in all infants of this group. This seems to explain the disagreement between this and the other groups. The author believes that practical measures designed to minimize the amount of liquor inhaled at birth would prevent the development of hyaline membrane atelectasis.

Infantile Nephrosis: Clinical, Biochemical, and Morphologic Studies of the Syndrome. H. G. Worthen, R. L. Vernier and R. A. Good. A. M. A. J. Dis. Child. 98:731-748 (Dec.) 1959 [Chicago].

The authors report on 12 infants in whom nephrosis developed during the first year of life and who were studied in the department of pediatrics of the Variety Club Heart Hospital in Minneapolis. Of the 12 infants, 7 were girls and 5 were boys. All the patients had the characteristic findings of the nephrotic syndrome, namely, edema, albuminuria, hypoalbuminemia, hypercholesterolemia, and elevation of the erythrocyte sedimentation rate. Microscopic hematuria was detected in at least one urine specimen from every patient. The symptoms, physical findings, and laboratory abnormalities were essentially the same as those of older children with idiopathic nephrosis. The infants, however, showed several unusual features, distinguishing them from the older children with the nephrotic syndrome: these features were the early age of onset (one month after birth in 6, and between the ages of 3 and 10 months in the other 6), a high familial incidence, refractoriness to treatment, and poor prognosis (8 of the 12 patients have already died).

Microscopic studies on biopsy or autopsy revealed varying degrees of glomerular fibrosis in the kidneys from 4 patients, while the kidneys from 5 patients did not show any glomerular abnormalities. The kidneys from the remaining 3 patients were of special interest microscopically, since a striking degree of dilatation of the proximal convoluted tubule was found. No cause for this unusual abnormal condition could be determined by microdissection of the kidneys. Electron-microscopic study of the glomeruli from 9 patients revealed fusion of the epithelial-cell foot processes. This abnormality of fine structure was identical with the lesion observed to the characteristic of older patients with nephrosis. The presence of this alteration of fine structure in glomeruli from patients with severe tubular dilatation suggests that the primary abnormality in the various patients with infantile nephrosis resides in the glomerulus.

No definite evidence is available at present to indicate whether or not the cause of infantile nephrosis is the same as that of idiopathic childhood nephrosis. The possible role of maternal toxemia has been discussed. The autoimmune mechanisms, which have been given etiological importance in childhood nephrosis by many workers, probably cannot be implicated as the cause of infantile nephrosis. The results of this study do not support the suggestion of other investigators that a metabolic defect, associated with crystalline deposits in the kidney, is the cause of infantile nephrosis.

A Case of Total Absence of Ganglion Cells in the Colon: Hirschsprung's Disease Without Megacolon. N. Genton and D. Pometta. Helvet. paediat. acta 14:383-395 (Oct.) 1959 (In French) [Basel, Switzerland].

The authors report on a 9-month-old girl with refractory constipation, repeated attacks of vomiting, and marked abdominal meteorism, who was admitted to the surgical department of the pediatric clinic of the University in Zurich, Switzerland, with a tentative diagnosis of megacolon (Hirschsprung's disease). Roentgenologic examination of the intestines with the aid of a barium enema revealed a normal diameter of the colon, an empty rectosigmoid, and the ascending, the transverse, and the descending colon filled with fecal material which could not be removed by repeated enemas or by the introduction of a rectal catheter. Laparotomy revealed a considerably dilated and hypertrophied ileal loop interposed between the intestinal wall and the cecum. The colon was not dilated. With the aid of a cecostomy the fecal material was removed from the cecum and the ascending colon. A biopsy of the cecal wall revealed total absence of ganglion cells. The cecostomy did not suffice to reduce the ileus. An ileostomy was performed, which reestablished the intestinal passage, but the condition of the infant deteriorated. Eventration with peritonitis occurred, and the patient died 6 weeks after her admission to the hospital.

This is a rare case of megacolon with total absence of ganglion cells in the colon. The diagnosis of aganglionic colon has been based on the history, the clinical picture, the roentgenographic findings, and the rectal biopsy. Only 2 cases of this type were collected from the literature; the patients were cured by an early ileostomy, followed after a few months by a total colectomy.

ENDOCRINOLOGY

Hyperinsulinism. R. Menguy. J. Oklahoma M. A. 52:797-804 (Dec.) 1959 [Oklahoma City].

The author reports on 2 men, aged 39 and 57 years, respectively, with organic hyperinsulinism, a symptom complex resulting from an excess of circulating insulin. In both patients the excess insulin was produced by a functioning tumor of the pancreatic islets of Langerhans. In the older man a prompt diagnosis was made, and full recovery resulted from distal pancreatectomy and splenectomy. The younger man was hospitalized repeatedly for recurrent attacks of unconsciousness, and a diagnosis of conversion reaction manifested by periods of amnesia and somnolence was made. One month later the patient, after having been comatose for 72 hours, was readmitted to the hospital, and this time a diagnosis of chronic brain syndrome of unknown cause and left cerebral cortical atrophy was made. After discharge the patient again had recurrent attacks of unconsciousness, lasting from 15 minutes to 5 days. He was rehospitalized, and a routine determination of the blood sugar level revealed a value of 29 mg. per 100 cc. The test was repeated, and a level of 33 mg. per 100 cc. was found. Only then a diagnosis of islet-cell tumor of the pancreas was made, and a round mass, 2 by 1 cm., was removed by wedge resection from the head of the pancreas. On microscopic examination of the operative specimen, the lesion was found to be a benign beta-cell adenoma. Despite successful removal of the functioning islet-cell adenoma, the patient had a poor result because of irreversible brain damage brought on by repeated severe hypoglycemic attacks. Unfortunately, throughout the patient's successive hospitalizations a psychiatric diagnosis served as a "mental block."

In most of the patients with organic hyperinsulinism, the results of surgical treatment are excellent. This is particularly true of those patients in whom the lesion is found at exploration, is single and benign, and can be removed by a partial pancreatectomy. Good late results can be expected in about 90% of the patients. When a blind distal pancreatectomy is performed because of failure to find a lesion, about 60% of the patients are cured of their symptoms, which can be summarized in the classical symptomatic triad (Whipple's triad) of attacks of hypoglycemic symptoms associated with fasting or exercise, accompanied by a blood sugar level lower than 50 mg. per 100 cc., and relieved by the administration of glucose. The most important aid to the diagnosis is an awareness on the part of the physician that hyperinsulinism may be responsible for such vague and unspecific symptoms as loss of consciousness, confusional state, weakness and fatigue, deep coma, sweating, drowsiness and stupor, lightheadedness, visual disturbances, amnesia, clonic convulsions, noisy behavior, and headache. In view of the nature of the presenting symptoms, it is not surprising that such diagnoses as epilepsy, psychosis, or inebriation are considered. Early diagnosis of this condition is of the utmost importance, because repeated hypoglycemic attacks may lead to irreversible brain damage. The only form of treatment is surgical.

Precocious Puberty Associated with Hepatoma. R. L. Reeves, H. Tesluck and C. E. Harrison. J. Clin. Endocrinol. 19:1651-1660 (Dec.) 1959 [Springfield, Ill.].

A boy, 8 years of age, was admitted to the hospital because of precocious sexual development, consisting of pubic hair, penis of adult size, many erections, and sore breast. There was no response to the cortisone suppression test. When first seen, evidence of gonadotropic activity was overlooked, and a tentative diagnosis of adrenal tumor was made in view of the increased excretion of urinary 17-ketosteroids. Both adrenals were explored through bilateral lumbodorsal incision, yielding no result. The patient was discharged, but readmitted 3 months later because of the presence of a hard epigastric, nontender mass. An abdominal exploration revealed a pseudoencapsulated tumor within the liver. A biopsy specimen was obtained, and the abdomen was closed. The patient died 20 days after the operation.

Microscopic study of the tumor indicated hepatic origin and suggested a hepatoma with a biliary duct component. At autopsy, no abnormal changes were found in the pineal gland, hypothalamus, or pituitary body, other than a possible increase in the number of amphophilic cells in the pituitary. Assay of the tumor showed that chorionic gonadotropic activity was present in a mean concentration of 2 I. U. per gram, net weight, of tumor tissue. This case represents a clear evidence of an endocrine disturbance from both clinical and laboratory standpoints. The tumor was almost certainly primary in the liver. It seems that this hepatic tumor had the capacity to elaborate gonadotropin—a function heretofore considered to be restricted to the pituitary, placenta, and chorionepithelioma.

Diabetes Insipidus Complicating Total Adrenalectomy. J. R. Rees and J. F. Zilva. J. Clin. Path. 12:530-534 (Nov.) 1959 [London].

The authors present the history of a woman who in 1947, at the age of 54 years, had undergone radical mastectomy and local irradiation because of carcinoma of the left breast. She remained well until 1957, when malaise, loss of weight, and bone pain developed. There was no local recurrence, but roentgenograms revealed extensive pulmonary and osseous metastases, involving the femurs, pelvis, and skull with erosion of the sella turcica. Oophorectomy and total adrenalectomy were performed. Recovery was uneventful with the daily administration of cortisone by mouth, but several months later, despite increasing the dose of cortisone to 125 mg. daily and taking extra salt, the woman's condition rapidly deteriorated, with mental confusion and dehydration.

Thirst and polyuria, together with dehydration and hemoconcentration, indicated diabetes inspidus, and treatment with vasopressin (Pitressin) tannate was started. The dehydration disappeared, and the blood pressure became normal, with weight gain, a positive fluid balance, and a fall in plasma protein and serum sodium levels. By the third day the patient's clinical state was satisfactory. She had received 1 ml. of Pitressin in oil intramuscularly each day (5 pressor units per milliliter), but from the 4th day on deterioration was observed. It was then discovered that aqueous Pitressin (20 pressor units per milliliter) had been given in error for the oily suspension of Pitressin and, despite a sixfold increase in dosage, had produced no effective over-all antidiuretic response. When this error was corrected, the diabetes insipidus was again controlled.

Later it was discovered that the dose of cortisone was insufficient to maintain a normal sodium balance in this patient. An unusually high dosage of steroid was required for maintenance, for the combination of endocrine effects proved difficult to treat. However, it appears that, if a satisfactory preparation of Pitressin is used, water balance is readily restored, and steroid dosage must then be adjusted according to the serum electrolytes and urinary sodium excretion.

Sarcoidosis and Hyperparathyroidism with Hypercalcemia: Special Usefulness of the Cortisone Test. J. M. Burr, J. J. Farrell and A. G. Hills. New England J. Med. 261:1271-1275 (Dec. 17) 1959 [Boston].

It has been discovered that in certain conditions giving rise to hypercalcemia and hypercalciuria excessive absorption of dietary calcium and elevated renal calcium clearance occur, and that in these conditions the administration of cortisone regularly restores normocalcemia and normocalciuria, provided that the excess of calcium is not due to hyperparathyroidism. A puzzling problem arises also when 2 conditions capable of causing hypercalcemia coexist; here, too, the response to cortisone may be helpful in diagnosis. This is demonstrated by the case history of a 57-year-old woman. The diagnosis of sarcoidosis was favored during her early period of hospitalization because of the coexistence of hypercalcemia and its sequelae, hyperglobulinemia and hepatosplenomegaly. However, the history of nephrolithiasis dating back 8 years, the hypertension, the rather low serum phosphorus concentrations, and especially the abnormally low value for the phosphorus reabsorption index necessarily raised the question of possible hyperparathyroidism. The failure of administered cortisone to affect the hypercalcemia and hypercalciuria was considered to exclude sarcoidosis as a cause of these, and led to the presumptive preoperative diagnosis of hyperparathyroidism. Surgical removal of a parathyroid adenoma, followed by prompt relief of hypercalcemia and hypercalciuria, confirmed the diagnosis of hyperparathyroidism and showed that the hypercalcemia had been caused by hyperparathyroidism. The diagnosis of sarcoidosis was established when histological evidence of the disease was obtained in the resected spleen and abdominal lymph nodes.

This is the third reported case of coexisting sarcoidosis and hyperparathyroidism with hypercalcemia. In a case presented by Snapper and associates in 1958, the diagnosis of sarcoidosis had already been established, but because of mild hypertension and persistently lowered serum phosphorus level with high renal phosphorus clearance, and because the patient's twin brother had had a parathyroid adenoma removed, coexisting hyperparathyroidism was suspected. Failure of the elevated levels of calcium in the serum and urine to fall under the influence of administered cortisone then led to exploration of the neck and removal of a parathyroid adenoma, with correction of the hypercalcemia and hypercalciuria. Westra and Visser earlier (in 1949) had described a patient with sarcoidosis, from whom a slightly hyperplastic parathyroid gland had been removed, with amelioration of the hypercalcemia. The authors emphasize the importance of the cortisone test in disorders accompanied by hypercalcemia.

Diagnostic Difficulties in Juvenile Hypothyreosis. C. Thorén and G. Sterky. Nord. med. 62:1607-1612 (Nov. 5) 1959 (In Swedish) [Stockholm].

Juvenile hypothyreosis often has an insidious onset and is difficult to diagnose, especially in patients without myxedema. High sedimentation reaction is an important symptom. Of 19 children with hypothyreosis seen in a 10-year period, 10 had sedimentation reaction over 20 mm. Electrocardiographic changes occurred in 8 cases. Marked constipation resistant to therapy is a prominent symptom. Iron-refractory anemia may be a symptom. The maximum pulse rate is probably lowered in the disease. Three cases in girls, aged 12 or 13 years, with high sedimentation reaction but otherwise different symptoms of hypothyreosis, are reported. In the instance with juvenile myxedema, with unspecific increase in the antistreptolysin titer, there were megacolon and kidney stone. The general lowering of the T waves was normalized during work, which indicates functional origin. Megacolon can occur in hypothyreosis without myxedema. One of the cases illustrates a typical disturbance in ossification, the so-called epiphysis dysgenesis, which is usually most characteristic in the head of the femur; marked regression resulted after a year's increased thyroid therapy.

Direct and Indirect Estimation of Pituitary Adrenocorticotropin Reserves in Man Following Adrenal Steroid Therapy. D. A. Holub, J. W. Jailer, J. I. Kitay and A. G. Frantz. J. Clin. Endocrinol. 19:1540-1552 (Dec.) 1959 [Springfield, Ill.].

The purpose of this study was to find out whether abnormalities in the storage and release of corticotropin (ACTH) take place in man after the administration of large amounts of adrenocortical steroids. Pituitary ACTH concentration was measured post mortem in 17 patients, 5 of whom were treated and 12 were not treated, with adrenal steroids before death. The mean pituitary ACTH concentration in the steroid-treated group was 99 milliunits per milligram, which value did not differ significantly from that in the untreated group. Individual values ranged from 28 to 228 milliunits per milligram. Neither the average daily dose of steroids nor the total duration of therapy appeared to be correlated with ACTH concentration in this group. The pituitary ACTH concentration in one patient of the steroid-treated group was relatively low (28 milliunits per milligram), although she received 3 times as large a total dose of steroids as any other patient. Pituitary histological structure appeared normal in all steroid-treated patients with the exception of the preceding one, in whom Crooke's changes were seen in the basophilic cells. Adrenal atrophy was marked in 4 patients of the steroid-treated group and was mild in 1.

The availability of ACTH for release was tested by using the adrenocortical inhibitor Su-4885 in 9 living persons. Four patients had received steroid therapy for prolonged periods of time, and 5 had not. The responses of 3 of the steroid-treated patients were similar to those seen in the control group. Pituitary ACTH insufficiency was exhibited by only one steroid-treated patient. The present findings suggest that most of the steroid-treated patients respond normally to stimulation of the pituitary gland. Depletion of pituitary ACTH might be found in patients who have received large doses of steroids over prolonged periods of time.

DERMATOLOGY

Griseofulvin in Treatment of Infections of Scalp Due to Microsporum Canis. M. Beare and D. Mackenzie. Brit. M. J. 2:1137-1140 (Nov. 28) 1959 [London].

The authors report on 50 children with various types of ringworm observed at the Royal Belfast Hospital for Sick Children, 19 of whom had infections of the scalp due to Microsporum canis. These 19 children were between the ages of 15 months and 12 years, and all were given griseofulvin orally in doses of 0.25 Gm. 3 times daily. The duration of treatment varied from 3½ to 10 weeks. Fungal invasion of the hair was stopped abruptly soon after the drug was given, and new areas of infection did not appear. Debris, probably intrafollicular, remained infected, and the organisms were recovered readily for long periods up to 14 weeks after treatment was started.

Wood's-light fluorescence usually disappeared in 1 to 6 weeks and, on the average, in 3 weeks. In only 1 of the 19 children was there any evidence of fluorescence at the tips of the hairs. In contrast to experiments on guinea pigs, in which fluorescence at the tips is common, fluorescent tips are only exceptionally found in children. In one rather unusual case in this series, however, fluorescence was observed 8 weeks after treatment was started; after the second week this fluorescence appeared at various distances from the surface of the scalp; positive cultures were obtained up to 12 weeks after the initiation of treatment; and microscopic examination often revealed a well-established infection in a nonfluorescent portion of hair. Only 2 of the 19 children had nausea, but it was not certain that the nausea recorded could be attributed to the drug. No other symptoms which might have been attributed to griseofulvin were observed.

None of the patients received any form of local application. Because this was a clinical trial in which the authors were determining the effects of griseofulvin alone, the children were told not to wash their hair or scrub the affected area. Future studies should be directed toward a method for the removal of infected debris. Such methods might include washing, scrubbing, and/or shaving the affected areas, and the application of local fungicides. It is apparent that, although griseofulvin is a most remarkable advance in antibiotic therapy, it is insufficient in itself to cure scalp ringworm (at least that due to M. canis) within a reasonably short period.

Griseofulvin in Treatment of Persistent Fungal Infections of the Skin. A. J. E. Barlow, F. W. Chattaway, K. G. Hargreaves and C. J. La Touche. Brit. M. J. 2:1141-1143 (Nov. 28) 1959 [London].

The authors report on 34 patients with persistent fungal infections of the skin who were treated with griseofulvin given orally in doses of 1 to 2 Gm. daily at the Royal Infirmary in Huddersfield and at the General Infirmary in Leeds, England. Of the 34 patients, 2 children with candidiasis and 1 man with tinea versicolor showed no clinical change as a result of treatment. In 2 men with typical cattle ringworm due to Trichophyton verrucosum, the primary lesions resolved over a period of 3 weeks, and it was felt that the duration of the infection was not significantly modified. Immediate symptomatic improvement resulted in one man with a vesicular infection of the instep due to T. mentagrophytes var. interdigitale, but scaling persisted for 5 weeks and viable fungus was present in the sole for 6 weeks. Reexamination during the next 3 months revealed the soles to be normal. In 2 patients with infection of smooth skin only by T. rubrum, each showed subjective improvement; scrapings became negative after 10 days and have remained so for 6 months in one patient, while in the other scrapings still remained positive after 3 weeks.

The remaining 26 patients had long-standing infection of multiple nails and skin by T. rubrum, previously resistant to numerous methods of treatment, including surgical avulsion of nails. They were treated with griseofulvin for periods of 3 to 20 weeks. Most of them improved, but in only one patient was the infection eradicated. Since griseofulvin is fungistatic and not fungicidal, its mode of action would seem to be by inhibiting fungal growth in its mycelial stage, so that infection is carried away by the outward growth of keratins. In the smooth skin the inhibitory effect of griseofulvin will cause the fungus to lose its foothold in the normal process of desquamation of soft keratin. Nail infection presents a different problem, since here keratin does not desquamate: hence it is necessary to wait for the nail to grow sufficiently for infection to be carried beyond the free edge. At least 4 months must be allowed for infection of finger nails to grow out, while well over a year would be required for infection to be eliminated from the nail of the big toe. Whether it would, therefore, be necessary to administer griseofulvin continuously or intermittently over such a long period can be proved only by trial and error.

Increasing use of griseofulvin will clarify the position about toxicity. In this series, 3 patients were unable to tolerate the drug, but despite noting some variation in the differential blood count, there is insufficient evidence to state that the drug has a toxic effect on the bone marrow. It is, however, important that this possibility is borne in mind. A combination of surgical removal of nails, with systemic administration of griseofulvin and possibly the subsequent use of topical fungicides, would offer the patient with chronic nail infection by T. rubrum the best chance of cure.

Colloid Degeneration of the Skin (Colloid Milium): A Report of Seven Cases. J. D. Guin and E. R. Seale. A. M. A. Arch. Dermat. 80:533-537 (Nov.) 1959 [Chicago].

The authors report on 7 patients with colloid degeneration of the skin (colloid milium), who were admitted over a 6-year period to the department of dermatology, Baylor University college of medicine, Houston, Texas. The patients were all men, ranging in age from 33 to 37 years. In general, this group of patients with colloid degeneration of the skin was similar to those described in the literature. The high incidence of this skin disease in southeast Texas can be attributed to the long summers and to the large number of fair-skinned people in this area. The pseudovesicles of colloid degeneration occurred over the ears, the malar region, and the posterior neck in some of the patients, but the dorsum of the hands—more often that of the left hand—was the most severely involved in all the patients. The greater involvement of the dorsum of the left hand can be explained by the exposure to the sun on the left while driving a car with the window down. None of the patients improved while on ascorbic acid therapy. One patient, however, showed definite improvement 6 months after the treatment with ascorbic acid had been discontinued; it was found that he had been indoors during this entire period. It seems, therefore, that the patient's improvement could be attributed to the avoidance of excess sunlight rather than to the ascorbic acid therapy. The cholesterol level in the blood was increased in 4 of the 5 patients tested. The significance of this finding remains to be determined.

UROLOGY

Gonorrhea Due to Penicillin- and Streptomycin-Resistant Strain. R. T. Bjørnstad and K. Noreik. Tidsskr. norske laegefor. 79:1167-1169 (Oct. 15) 1959 (In Norwegian) [Oslo].

A case of acute gonorrhea, which an aviator had contracted in Japan, was treated at the Rikshospital in Oslo. The patient had had symptoms of acute gonorrhea for 6 or 7 days. Both the clinical course and the lack of response to penicillin and determination of resistance indicated that the gonococcic strain was resistant to penicillin and streptomycin. This was borne out when treatment for 5 days with a total of 2 million units of penicillin and 2.5 Gm. of streptomycin was without avail. The condition also remained unchanged after the injection of 600,000 units of procaine penicillin. However, treatment with a total of 9.5 Gm. of tetracycline gave good results. Because of increased communication between the Far East and Norway, more rapid spread of gonococcic strains, such as the one isolated in this case, is probable, with possible introduction of the disease into Norway in its incubation period. For gonorrhea patients infected in the Far East, Epstein advocates 900,000 units of procaine penicillin G administered twice daily at 3-hour intervals for 3 days, or a total of 5.4 million units.

Comparative Bacteriologic Study of Urine Obtained from Children by Percutaneous Suprapubic Aspiration of the Bladder and by Catheter. C. V. Pryles, M. D. Atkin, T. S. Morse and K. J. Welch. Pediatrics 24:983-991 (Dec.) 1959 [Springfield, Ill.].

A comparative bacteriological study of urine obtained by catheter and by suprapubic aspiration was performed in a group of 42 children who were presumed free from clinical infection of the urinary tract, and who were undergoing elective surgery for conditions that did not involve manipulation of the urinary tract. There was complete diagnostic correlation between urine obtained by suprapubic aspiration and the clinical impression; there was 92.8% diagnostic correlation between the first few milliliters of urine obtained by catheter (C_1) and the specimens obtained by suprapubic aspiration; and there was a 97.5% diagnostic correlation between the second few milliliters of urine obtained by catheter (C_2) and the suprapubic specimens. Three patients had significant bacterial counts in specimens obtained by catheter, and on this basis alone a diagnosis of pyelonephritis might have been made erroneously. The C_2 specimens, however, showed a significant count in only one of the 3 patients, pointing out the importance of discarding the initial few milliliters of urine obtained by catheterization. In this patient, the suprapubic specimen was sterile, the C_2 specimen grew out 3,100 colonies of Escherichia coli per milliliter of urine, while a subsequent clean voided specimen did not exhibit significant growth. The patient remained in good health, and in view of the sterile specimen obtained by suprapubic aspiration, the authors believe that the organisms grown in the C_2 specimen were due to contamination. Gram stains of all specimens were negative for organisms.

On follow-up examination 1 to 5 months after the operation, all the patients were found to be free from infection of the urinary tract within a period of 4 to 6 months after catheterization. The authors believe that, while properly collected, clean voided specimens may be used in most instances for making the diagnosis of true bacteriuria in children, catheterization, when properly done, should not be withheld for fear of producing infection of the urinary tract. It must remain a necessary procedure in the diagnosis and management of infections of the urinary tract in the following cases: those in which there is urinary retention; those in which repeated study of clean voided specimens yields borderline or doubtful results; those in which the patient is so acutely ill that there is need for immediate antimicrobial therapy and no time for multiple specimens to be obtained; or those in which the patient is unable or unwilling to cooperate.

Prostatectomy: A Survey of 2,000 Cases. C. B. Thrasher and P. M. Beglin. California Med. 91:338-340 (Dec.) 1959 [San Francisco].

A statistical analysis was made of 2,000 consecutive cases in which prostatic operations were performed in the period from 1947 to 1957 at the Southern Pacific General Hospital, San Francisco. The operations included transurethral resection which was done in 1,327 instances; suprapubic prostatectomy, in 614; perineal prostatectomy, in 43; and retropubic prostatectomy, in 16. The mortality rates were lowest for transurethral resection (1.8%) and highest for retropubic prostatectomy (6.25%). Coronary artery disease and pulmonary embolism were the chief causes of death. It was generally felt that preliminary partial vasectomy previous to transurethral resection added very little to successful convalescence. Although distilled water was used routinely for irrigation during transurethral resection, there was no incidence of lower nephron nephrosis. The incidence of recurrence of prostatic obstruction was highest by far after transurethral resection.

Carcinoma of the Prostate with Metastases to the Testicle. C. Ney, J. J. Roth and C. A. Lopez. A. M. A. Arch. Surg. 79:1028-1031 (Dec.) 1959 [Chicago].

The authors report on an 85-year-old man with carcinoma of the prostate with metastases to the testis, who was admitted to the Morrisania City Hospital in New York, and on a 55-year-old man with secondary carcinoma of the testis arising from carcinoma of the prostate, who was admitted to the Lebanon Hospital in New York. In the first patient a transurethral resection of the prostate had been performed previously with removal of 11 Gm. of tissue; microscopic examination of the operative specimen revealed moderate glandular hyperplasia with fragments of adenocarcinoma of the prostate. The patient was advised to have an orchiectomy, which he refused. Seven years later he was readmitted to hospital, complaining of nocturia. This time bilateral orchiectomy was performed, and microscopic examination of the operative specimens revealed atrophy of the right testis, and in the left testis a well-differentiated adenocarcinoma of the same type as seen in the prostate previously. In the second patient a transurethral resection of the prostate had also been performed previously, with removal of 20 Gm. of tissue; microscopic examination of the operative specimen revealed nodular hyperplasia with fragments of papillary adenocarcinoma. Five years later, the patient was readmitted to hospital because of a 2-month history of discomfort in the left lower quadrant. For about one month he had noticed that the left testis had become hard and painful. A bilateral orchiectomy was performed. Microscopic examination of the operative specimens revealed metastatic papillary adenocarcinoma of the left testis, showing a similar pattern to that previously observed in the prostate.

The testis may become the seat of secondary tumors by any of 5 routes, i. e., by retrograde venous extension or embolism; by retrograde lymphatic extension; by arterial embolism; by way of the lumen of the ejaculatory ducts to reach the epididymis and testis; and by direct extension through the vas deferens but not within the lumen of the vas. The 2 patients did not show any involvement of the cord with tumor, and the authors assumed that metastases occurred by way of arterial embolization. Twenty-six previously published cases of secondary carcinoma of the testis arising from carcinoma of the prostate were collected from the literature. It is suggested that, even though this lesion has occurred rarely in the past, it may be found even less frequently in the future.

Cranberry Juice and the Antibacterial Action of Hippuric Acid. P. T. Bodel, R. Cotran and E. H. Kass. J. Lab. & Clin. Med. 54:881-888 (Dec.) 1959 [St. Louis].

Cranberry juice has been widely used in the Cape Cod area of Massachusetts in the treatment of infections of the urinary tract. Investigators had demonstrated that the urinary excretion of hippuric acid rose after the ingestion of cranberries (the berries of Vaccinium macrocarpon) or of cranberry juice. The structural similarity of hippuric acid to mandelic acid, which inhibits bacterial multiplication, was another indication that substances from cranberries might have antibacterial activity. The studies described were undertaken to investigate the antibacterial activity of hippuric acid and the effect of ingestion of cranberry juice on urinary acidity and hippuric acid excretion. Commercial cranberry juice, consisting of one part juice from pressed cranberries and 2 parts water, with added sugar, was used. It was found that cranberry juice, given in maximal tolerable amounts to normal subjects, increases the acidity of the urine slightly and increases the hippuric acid content of the urine by several grams a day. Hippuric acid, in concentrations of 0.02 to 0.04 M, is bacteriostatic at pH 5.0 for the common pathogens of the urinary tract, and its activity decreases about fivefold as the pH is raised to 5.6. Only occasionally does cranberry juice contribute enough hippuric acid to the urine to achieve concentrations which are bacteriostatic at pH 5.0. Hippuric acid, in doses of 12 to 14 Gm. per day, usually lowers the pH of the urine to 5.2 or less, and is excreted in sufficient concentration to induce inhibition of bacterial growth in urine at this pH. The data suggest that the use of hippuric acid as a urinary antiseptic deserves further study.

Nephrectomy in Cases of Hypertension. J. G. Yates-Bell. Brit. M. J. 2:1371-1375 (Dec. 19) 1959 [London].

Sixty-six patients underwent nephrectomy for unilateral renal disease associated with hypertension. These patients were divided into 3 groups: (1) 36 patients with hypertension; (2) 20 hypertensive patients with urinary disease; and (3) 10 patients, under 40 years of age, with urinary disease and slight hypertension. The criterion for considering the result as a cure was a reduction of 20 to 25%, plus a fall to 90 or 100 mm. Hg, in the diastolic pressure. The operation was successful in 12 patients (33.3%) in group 1, in 10 in group 2, and in 8 in group 3 (including 5 children under 14 years of age. The total percentage of cures, taking as a criterion the requirement of a 20% reduction in blood pressure, was 45.5%. In addition, some patients who did not fulfill the established requirements to be considered cured received durable benefits from the point of view of the hypertension. Hydronephrosis was the most frequent condition in this series and obtained the highest percentage (54%) of cures. The average age of the 14 patients with hydronephrosis who were cured was 29 years, whereas the average age of the 10 who were not cured was 44. The average age of the 5 patients with pyelonephritis who were cured was 18 years, and that of the 8 patients who were not cured was 44. The 8 children under 14 years present in the whole series were cured. The average age of the 30 patients successfully treated was 34 years, and the average age in the 36 failures was 44.

The author suggests that a diastolic pressure of 90 mm. Hg during one year should be required in order to claim a good result of nephrectomy for hypertension. However, patients who have been symptomatically cured for 3 years, with a 20% fall in the diastolic pressure, should also be included in the good-result group. The requirement of a maximum of 100 mm. Hg diastolic pressure is too lenient, whereas the requirement of a 25% reduction is too severe.

OPHTHALMOLOGY

Vitreous Opacities Diagnostic of Familial Primary Amyloidosis. H. E. Kaufman and L. B. Thomas. New England J. Med. 261:1267-1271 (Dec. 17) 1959 [Boston].

The authors call attention to the presence of vitreous opacities in primary amyloidosis, pointing out that Kantarjian and DeJong in 1953 first described vitreous opacities in a family with amyloidosis, and several other observers have reported similar cases. The authors report 2 patients in whom such vitreous opacities and loss of vision began 4 and 13 years, respectively, before any detectable systemic signs or symptoms of amyloidosis. Because these opacities had been seen only in familial primary amyloidosis, the case of the brother of one of the patients was investigated. He had died with gastrointestinal symptoms, a progressive and bizarre neuropathy, and finally congestive heart failure, but the diagnosis of amyloidosis had not been made clinically or on postmortem examination. Only upon reexamination of tissues from this patient were the massive deposits of amyloid that caused his death apparent.

Observations on the formation of vitreous opacities in primary amyloidosis suggest that they begin first around retinal blood vessels, causing an apparent perivasculitis. Later, the deposits accumulate near the vascular ciliary processes, then retrolentally and in the posterior vitreous, and finally they affect the central vitreous. Patients with amyloid vitreous occasionally have a sudden loss of vision after minimal trauma. This appears to be caused by a detachment of the vitreous body from its adhesions to the optic disk and posterior retina, resulting in a clumping of this opaque material in the visual axis.

In the hope that removal of the opacities might restore vision to otherwise apparently normal eyes, the authors attempted vitreous transplantation on 6 eyes of 4 patients. Only a small amount of opaque vitreous could be removed from 5 eyes in spite of vigorous attempts at withdrawal and lavage. Failure to remove the opacities seemed to be due to the fact that they are bound to the fiber structure of the vitreous. The authors comment on the differences between sporadic and familial primary amyloidosis, pointing out that vitreous opacities occur almost always in the familial type of amyloidosis. The finding of these vitreous opacities should suggest that not only the patient under observation but others in his family may be afflicted with primary amyloidosis.

Observations on Compensatory Adjustments in One-Eyed Persons. E. Zagora. Brit. J. Ophth. 43:596-600 (Oct.) 1959 [London].

The author reports observations on 140 one-eyed persons observed over a period of 8 years. These patients had normal, or nearly normal, vision in the remaining eye and no anomalies of the ocular movements. They were mostly persons who had lost one eye in childhood or in adult life through injury and were wearing a prosthesis. Patients with one amblyopic eye were not included in this series. In order to adjust themselves to the new visual conditions after the loss of one eye, many persons tend to assume a persistent compensatory head posture, which may be called "uniocular torticollis." The abnormal head postures adopted by one-eyed people may be classified as: tilting the head; turning the face; and depressing the chin. Persistent tilting of the head toward the chest represents an attempt to extend the relative field of vision. The face is usually turned toward the side of the lost eye. This has 2 advantages: 1. The nasal half of the visual field of the remaining eye is extended. 2. The remaining eye assumes temporarily the midposition of a single frontal visual organ. This alignment can give the one-eyed person information on the position of objects in space in relation to the median vertical plane through the body, and so helps him to undertake work in which symmetrical exactitude is important. Lowering the chin extends the field of vision of the remaining eye, especially in the lower nasal quadrant. Depressing the chin toward the chest causes the remaining eye to become slightly elevated in the orbit.

In fitting a one-eyed person with spectacles for the correction of refractive errors, care must be taken that the bridge, frames, and side-pieces are so designed as not to restrict any part of the nasal field of vision of the remaining eye. These measures will help the one-eyed person to hold his head straighter. If the nose is large, a plastic operation may improve the visual field, so that the compensatory head-tilt and face-turn become less pronounced. A few one-eyed persons (especially those who have been left with the dominant eye) have reported that they find it necessary to close the lids of the lost eye when looking at very distant objects or in difficult visual conditions, such as fog, rain, and reduced illumination. The lid closure appears to be carried out involuntarily.

Investigations on Clinical Aspects and Etiology of Epidemic Keratoconjunctivitis. R. Zintz and O. Vivell. Klin. Monatsbl. Augenh. 135:521-533 (no. 4) 1959 (In German) [Stuttgart, Germany].

In the region of Freiburg im Breisgau in south Germany, keratoconjunctivitis has occurred in recent years in epidemic form as well as sporadically. This gave the authors the opportunity to study its clinical and serologic aspects in 70 patients. In 50 of the 70 patients the keratoconjunctivitis took a typical course. The majority of these patients contracted the disorder in the course of an epidemic in a sanatorium. The incubation period ranged from 7 to 10 days. Irritation and foreign-body sensation were usually the first subjective symptoms. Conjunctival irritation and increased secretion were the first objective signs, and a few patients had swelling of the lid. In the further course, the conjunctival hyperemia increased, and sago-like nodules appeared. Chemosis and petechial hemorrhages in the conjunctiva were observed in some of the patients. Threads of grayish mucus with leukocytes could be observed in the conjunctival secretion. Swelling of the preauricular lymph nodes on the involved side occurred in all 50 patients 2 or 3 days after the onset of symptoms. In 47 of the 50 patients in whom the cornea became involved, the signs of irritation became more severe between the 7th and 12th days. Healing of the corneal infiltrations took place between the 13th and 26th days. The second eye usually became involved from 3 to 16 days after the onset, but the process was abortive in the second eye in 39 of the 50 patients, and in 26 of the patients the cornea of the second eye did not become involved. In the other 20 patients the course of the keratoconjunctivitis was atypical.

The results of the laboratory test on the 70 patients were compared with those on 10 healthy patients, serving as controls. The adenovirus complement-fixation test and the type-specific neutralization test against adenovirus, type 8, were performed. In 36 of the typical cases the complement-fixing antibodies increased during the course of the keratoconjunctivitis. In 16 of these 36 patients the neutralization test against type 8 adenovirus was carried out, and a conclusive increase in titer was observed in 8 of the 16 patients; in the other 8 patients the titer suggested that type 8 adenovirus was probably the etiological agent.

Among the 20 patients with atypical course, there were only 3 in whom the complement-fixing antibodies increased, and in 2 others the presence of neutralizing antibodies seemed probable. No serologic changes were observed in the 10 controls. The authors point out that type 8 adenovirus has been isolated from patients with the typical form of epidemic keratoconjunctivitis in many countries during the last several years. Transmission is frequently iatrogenic, probably by ophthalmological instruments and solutions. The conjunctiva seems to be a portal of entry for virus infections, but the authors suggest that at least in epidemic keratoconjunctivitis it might also offer a route for prophylactic measures. There are no recurrences after keratoconjunctivitis. It is suggested that the condition might be prevented by applying specific convalescent serum to the conjunctiva. Involvement of the other eye could also perhaps be prevented in this way.

OTOLARYNGOLOGY

Fatal Granulomatosis of the Respiratory Tract (Lethal Midline Granuloma-Wegener's Granulomatosis). I. M. Blatt, H. S. Seltzer, P. Rubin and others. A. M. A. Arch. Otolaryng. 70:707-757 (Dec.) 1959 [Chicago].

Data on 124 cases of lethal midline granuloma-Wegener's granulomatosis are presented—112 from the medical literature and 12 from the University of Michigan Medical Center in Ann Arbor. It is suggested that the rhinopharyngologic-midfacial disease, described by Stewart, and the rhinologic-systemic syndrome, described by Wegener, are one and the same disease process—a granulomatous necrotizing angiitis, primary in the respiratory tract with systemic involvement and invariably fatal. Through concentration of case material it has been possible to formulate the clinical manifestations of the period of active disease and to observe the effects of various methods of treatment. Surgical intervention appears to increase the morbidity and intensity of the ulceronecrotic destructive process in the midfacial and other areas of the body, thereby creating deformities shocking to behold. When adrenal steroid therapy is used, the patients are apparently spared the frightful destruction of bone and soft tissue, particularly in the facial area, so that the face remains intact.

The over-all therapeutic response is usually dramatic within a few days, and it is possible to extend the lives of these seemingly doomed people by months or even years. The antibacterial activity of the antibiotic drugs has been invaluable in eliminating secondary invaders. Ionizing irradiation may find its effectiveness in the treatment of this inflammatory lesion. Clinical, histological, and preliminary laboratory evidence is presented to suggest that the lethal midline granuloma-Wegener's granulomatosis complex is a hypersensitivity reaction evoked by an autoantigen-antibody mechanism.

Two New Methods for the Assessment of Central Auditory Functions in Cases of Brain Disease. J. Matzker. Ann. Otol. Rhin. & Laryng. 68:1185-1197 (Dec.) 1959 [St. Louis].

Present-day hearing tests (threshold audiograms, tuning-fork tests, speech tests, and recruitment measures) are not designed to give information about the state of the central portion of the auditory system. Matzker calls attention to the new methods for the assessment of central auditory functions developed by Bocca, of Milan, and to the test for sound localization described by Sanchez-Longo and Forster. He describes his own methods, namely, (1) the binaural test, which is based on the principle of binaural fusion, and (2) his test for sound localization, which employs a method of interaural time differences. He has used the binaural hearing test (bilateral integration) in more than 1,700 patients and the sound localization test in more than 400 patients. These tests appear to provide audiometric tools for the exploration of the central auditory pathways. The test results not only indicate that a central lesion is present but also, within limits, point to the location of such lesion. While a high score of mistakes in the binaural test is indicative of a functional failure of the synaptic connections within the brain stem, the deviation of the localization band to one side points to a cerebral lesion on the contralateral side or to a brain-stem lesion on the homolateral side. It appears that the dividing level above which contralateral localization, and below which homolateral localization, occurs is the ventral brain stem. In each individual case one has to make sure that a deviation observed was not caused by a unilateral peripheral impairment.

In contrast to the results obtained by Sanchez-Longo and Forster, the results of Matzker indicate that the occurrence of abnormal lateralization of sound is not limited to patients with pathological processes in the temporal lobe. When his modification of the testing technique is used, processes located in the frontal, parietal, and occipital lobes have also been found to contribute to an abnormal localization.

A New Technique for Stapes Mobilization. B. Cornish. J. Laryng. & Otol. 73:738-744 (Nov.) 1959 [London].

Stapes mobilization is now an established technique, and it is no longer the freeing of the footplate which is on trial but the various methods of achieving this. The author found that in the patients in whom he failed to achieve mobilization by the Rosen technique of pressure, applied to the region of the neck of the stapes, the cause was usually the inability to determine the anatomically correct line of force. This seemed to be due in most cases to the fact that the stapes was lying obliquely in 2 different planes. The same difficulty presented itself in mobilizing the footplate directly, and was enhanced by the inability to see the footplate clearly in many instances. These difficulties led to the study of variously sectioned temporal bones, from which it appeared that the ideal direction of force of any maneuver to mobilize the footplate must be in the line of the stapedius tendon. Working on this principle, the tendon was always fully exposed before attempting mobilization. This, in turn, led to further consideration of the mechanics of the stapedius muscle and the stapes. It seemed that, if the stapedius could be made to contract with sufficient force, it would possibly produce mobility of the stapes, or a fracture at an anatomically suitable site. Dissection of the stapedius showed that it usually has a bulk of muscle fibers which could exert a strong pull, if stimulated electrically. Faradic current was thought to be the most suitable as being nonpolarizing to the muscle.

The technique of the stapedial mobilization by electrical stimulation of the stapedius muscle is described. It has been successful in a significant number of cases. These are admittedly short-term, and the series is too small for any percentage results to be evaluated. However, it is not intended at this stage to prove that the results will be maintained, or that the hearing gain is any greater by this method, but rather that mobility can be achieved by simple physiological methods in a significant proportion of cases. The standard methods must still be resorted to in certain cases, but it is felt that this electrical stimulation is a well worthwhile initial maneuver in all cases of stapedial fixation.

Oral Cancer in Women: A Study of the Increasing Incidence. W. W. Dalitsch and S. J. Vazirani. Am. J. Surg. 98:869-874 (Dec.) 1959 [New York].

The impression that cancer of the oral cavity in women is increasing in frequency was obtained by the authors in the wards or clinics of the Cook County Hospital and the Research and Educational Hospitals in Chicago. To substantiate this clinical impression, they studied the records of these hospitals, which demonstrated this increase. Other investigators have found a similar trend. This increased incidence is associated with an increasing use of tobacco by women and suggests a causal relationship. A long duration of exposure to the use of tobacco prior to onset of symptoms is a consistent finding in women with oral cancer. To prevent oral cancer, physicians must educate their patients to avoid harmful habits, such as smoking; to seek early advice and aid, if any abnormality is suspected; and to practice self-examination of the oral cavity. They must also help to discover and remove, or correct, noxious influences, such as neglected oral hygiene; chronic dental infection and inflammation; mechanical, thermal, actinic, and chemical irritants; and early lesions, such as leukoplakia and benign growths.

Current Treatment of Sinusitis. K. M. Simonton. Journal-Lancet **79**:535-537 (Dec.) 1959 [Minneapolis].

Simonton, of the Mayo Clinic, points out misconceptions on the part of patients about sinusitis and discusses anatomic and physiological aspects of the nasal sinuses. Sinusitis is divided into the acute, subacute, and chronic forms. Acute sinusitis is a self-limiting disease, usually accompanied by acute infection in the nasal mucosa. Symptoms are malaise, nasal obstruction, serous to purulent discharge, and pain and tenderness in the region of the affected sinuses. Subacute infection results when resolution of acute inflammation is delayed by factors that impede drainage from the sinuses, such as septal spur or cystic turbinate, or pathological changes, such as edema, inflammatory swelling, or polyps. The symptoms are purulent or mucoid drainage; obstruction, which may be relieved by discharge of secretions; cough; pharyngitis; and sense of pressure in the face. Pain is unusual. Chronic infection supervenes as a result of irreversible changes which permanently impair the drainage of the sinus. This may follow a single severe infection or repeated episodes of acute infection. Common changes are metaplasia of the epithelium with loss of cilia, subepithelial fibrosis, and vascular changes. The end-result is fibrosis, which may be manifested as either atrophy or thickening of the tissues. Symptoms are persistent drainage and repeated respiratory infections. Pain occurs only with changes of pressure within the sinus.

The treatment of acute sinusitis starts with rest and supportive measures. Adequate warmth and humidity aid in putting the nasal mucosa at rest. Sulfonamides are inactivated by pus and are of limited value in sinusitis. Most organisms causing acute infections of the upper part of the respiratory tract are sensitive to penicillin and the broad-spectrum antibiotics, so that treatment can be started with any of these drugs, pending results of culture. The dosage should be adequate to reach organisms situated in purulent exudates in the sinus, and should be at least double the dosage used for infection in tissues. Use of the drug should be continued until cultures are negative, or until well after all symptoms have abated. Local therapy with vasoconstricting drugs aids drainage, but use of these drugs should be limited to 5 to 7 days to avoid drug-induced edema of the mucosa. Local heat aids in relief of pain and congestion, and small doses of roentgen rays are effective for relief of severe pain arising from acute sinusitis. Surgical treatment is contraindicated in acute infection except for trephination of the frontal sinuses in fulminating infection.

In subacute infection antibiotic drugs are best administered under bacteriological control. Lavage is the most effective treatment. The maxillary sinus is most subject to subacute infection. Evacuation of the reservoir of pus in this sinus usually allows resolution of infection in the frontal and ethmoidal sinuses.

In many cases of chronic sinusitis surgical treatment must establish new drainage pathways or eliminate factors obstructing drainage. The maxillary and sphenoidal sinuses present large areas of common wall with the nasal chamber. Removal of this wall provides a large opening for drainage, which seldom closes postoperatively. The walls of the ethmoid cells may be removed to create a cavity with free communication with the nose. In the frontal sinus the surgically created drainage pathway is long and narrow and must be lined with epithelium to prevent closure, preferably with nasal mucosa. Sinusitis is frequently found in association with chronic bronchiectasis, bronchitis, and asthma. Elimination of a focus in the sinuses may control, but seldom cures, infection in the lungs. The results of treatment of infection of the sinuses are gratifying.

The Treatment of Recent Bell's Palsy on a Rational Etiological Basis: Results of Cervical Sympathetic Block and Corticosteroid Therapy. F. B. Korkis. A. M. A. Arch. Otolaryng. **70**:562-569 (Nov.) 1959 [Chicago].

The author feels that the neurovascular theory offers the best explanation for paralysis of the facial nerve (Bell's palsy). It explains the sudden onset of the condition, the lack of general constitutional disturbance, the variability in the degree of severity of the paralysis, the differences in the time and degree of recovery, the possible precipitation by exposure to draft, the progression which is sometimes seen from an incomplete to a complete paralysis (secondary compression), and the possibility of recurrence. Mild cases are compatible with minor degrees of temporary spasm, and severe ones with long-lasting spasm, or thrombosis. The author summarizes observations on 65 patients with atraumatic facial palsy. This number included 7 patients with geniculate herpes (herpes oticus), which condition had been referred to as "Bell's palsy," although subsequently its true nature was established. These patients formed a control group, because herpes oticus is not a vasospastic process.

While formerly Bell's palsy was considered as requiring no active measures apart from reassurance, support of the paralyzed musculature, and physical therapy to maintain muscle tone, such an expectant outlook is outmoded today in the light of the neurovascular hypothesis. Rational treatment aims at rapid relief of angiospasm, prevention of secondary thrombosis, and reduction of swelling. Rapid vasodilatation is brought about by paralysis of the cervical sympathetic system by a stellate block. This can be accomplished by injecting a 1% solution of procaine into the vicinity of the ganglion. Cortisone is capable of reducing tissue edema in the absence of definite infection.

Stellate blocks, repeated at intervals of 2 or 3 days, were used by the author in some patients with Bell's palsy. In other cases he used cortisone, either in combination with cervical sympathetic blocks or as the sole therapeutic agent. Patients with Bell's palsy, who were treated with physical therapy, heat, and exercises, served as controls, together with the aforementioned 7 patients with herpes oticus.

The aim of this study was to determine the treatment most likely to give the greatest degree of recovery in the shortest possible time and to test the validity of the ischemic theory of origin of Bell's palsy. Vasodilatation, produced by paralysis of the cervical sympathetic system by shortening the duration and severity of the paralysis, was most effective; this supports the vasospastic hypothesis. Corticosteroid therapy was not combined with stellate blocks in most cases in this series because the author wished to determine the effectiveness of one form of therapy. However, the 2 treatments should be combined, for by the one vasospasm is relieved, and by the other secondary edema is reduced. There is still a place for decompression of the facial nerve in patients who fail to respond to this regimen, but this operation will be required less often than formerly. Decompression must be performed before prolonged edema has caused nerve atrophy.

The author feels that patients with Bell's palsy should be under the care of an otologist, for the diagnosis demands an examination of the auditory system to exclude other peripheral causes of facial paralysis. The otologist also is fitted to perform a stellate block, which is the logical treatment for the early case, and by following the course, he is in a better position to judge when decompression is needed.

Repair of Ossicular Defects with Ostamer. J. Sataloff. A. M. A. Arch. Otolaryng. 70:415-418 (Oct.) 1959 [Chicago].

The author used Ostamer, a polyurethane foam, at first in the ears of 25 cadavers in which defects were created in various parts of the ossicular chain. In repairing these ossicular defects, Ostamer was prepared by mixing together a viscous prepolymer with a viscous catalyst in the ratio of 4 to 1. The resultant mixture is a thick, extremely adhesive substance from which carbon dioxide and heat are liberated. On hardening, it swells to twice the original volume to form a very light porous plastic. Ostamer successfully restored the continuity of the ossicular chain in the ears of the cadavers. After this "practice period," Ostamer was used in 2 living patients, a 14-year-old boy and a 45-year-old woman.

The first patient had had a marked hearing impairment for 9 years after a right simple mastoidectomy. Two attempts to repair a large defect between the head of the stapes and the absent long process of the incus, which had probably been inadvertently damaged in the course of the mastoidectomy, with the aid of small pieces of bone or fibrous tissue had failed. A drop of Ostamer was placed on the stapedial head, and the end of the incus was pressed into the drop until it hardened. Results of a preoperative audiogram and one taken one week postoperatively indicated a substantial hearing improvement. In the second patient, who claimed unilateral insidious deafness for 3 years, the absence of the incus and a large perforation in the eardrum made columelization the procedure of choice. In preference to placement of a graft over this perforation, a drop of Ostamer was placed over the head of the stapes, and the edges of the perforation were embedded into the Ostamer filling the defect. There was a substantial improvement in hearing one week after the operation.

While Ostamer in its present form has been used to advantage in the repair of ossicular defects, it would be desirable that the material be modified, if possible, to prolong the hardening time and increase the elasticity.

PATHOLOGY

The Relation of the Morphology of Gastric Carcinoma to Long and Short Term Survival. C. H. Urban and G. McNeer. Cancer 12:1158-1162 (Nov.-Dec.) 1959 [Philadelphia].

The authors report on 25 men and 13 women who had survived more than 5 years after total or partial gastrectomy for cancer of the stomach (long-term survivors), and on 33 men and 20 women who had died of cancer of the stomach one year after the operation. Of these 91 patients from the Memorial Center for Cancer and Allied Diseases in New York, 74 were between the ages of 50 and 80 years, 14 were between the ages of 20 and 49 years, and the ages of 3 were unknown. The morphologic features associated with each of the patients were determined from the description of the gross operative specimen and its microscopic appearance. In general, the cancers of the 5-year survivors were small, superficial tumors of low histological grade, growing in a circumscribed fashion, and had not given rise to lymphatic metastases. Signet-ring cells made up only a minority of the tumor cells in these patients. By contrast, the patients who survived less than one year had larger tumors of high histological grade which penetrated diffusely and deeply into the gastric wall. Lymphatic metastases were generally present, and most of the tumor cells were of the signet-ring type.

The factors that differed most between the long-term and short-term survivors were pattern of growth, depth of penetration of the tumor into the gastric wall, and involvement of lymph nodes by metastases. These are considered to be useful prognostic criteria. Of these 3 factors, pattern of growth was by far the most striking one separating long-term and short-term survivors. Patients who survived more than 5 years with large cancers were found to have tumors exhibiting the "en bloc" pattern of growth. The long-term survivors with large tumors that exhibited the mixed pattern of growth also had tumors confined to the gastric wall which had not metastasized to lymph nodes. If a patient had a small cancer and died in less than one year, the cancer usually showed the signet-ring-cell pattern of growth and had penetrated through the serosa. These findings would appear to confirm the growth pattern as a fundamentally important characteristic of tumor morphology. It appears that certain features, such as increasing depth of penetration and increasing grade, are definitely associated, whereas depth of penetration and presence of lymph-node metastases appear to be independent of each other. Despite the numerous interrelationships that could be demonstrated, no clear pattern emerged which could be set down in the form of general rules for prognosis.

The Value of Routine Serologic Tests for Syphilis on Hospital Admission. R. E. Bell. Am. J. Clin. Path. 32:521-525 (Dec.) 1959 [Baltimore].

In many hospitals a serologic test is routinely administered to each adult patient admitted. Of 13,372 routine tests for syphilis in a large general hospital, 141 tests (1.06%) were reported positive. These represented 106 patients. The discovery of a positive serologic test for syphilis led to the diagnosis and treatment of 5 or possibly 6 persons. Of the 6 treated or probably treated, one was admitted to a mental hospital with neurosyphilis, and another died of advanced cardiovascular disease within a year. The maximal number of diseased persons discovered and successfully treated, therefore, was 4. The cost of finding these 4 has been estimated at $1,600 per case.

One-third of the positive reactors were more than 65 years of age. None of these had active disease or were treated, and the author feels that routine testing of older patients should be discontinued. However, although the number of new and unsuspected cases likely to be discovered by routine blood testing is very small, the clinical importance of the discovery cannot be overlooked. In addition, the information (pertaining to all positive tests) which is routinely sent to public health authorities is important for the maintenance of their records. Thus, continuation of the policy of routine testing on all hospital admissions, except children and those more than 60 years of age, may well be worthwhile.

Diagnosis of Clinical and Subclinical Salmonellosis by Means of a Serologic Hemagglutination Test. E. Neter, A. M. Drislane and A. H. Harris. New England J. Med. 261:1162-1165 (Dec. 3) 1959 [Boston].

A combined bacteriological and serologic study on patients with enteritis due to Salmonella organisms and their contacts revealed the occurrence of subclinical infection. Subclinical infection was diagnosed on the basis of a specific antibody (hemagglutinin) response of the subjects of study in the presence or absence of the pathogen in the feces. It is postulated that 2 types of Salmonella carriers exist, one associated with disease, clinical or subclinical, resulting in a specific antibody response, and the other without antibody response. The latter type of carrier is considered a "lumen" carrier. On the basis of the data obtained, it is suggested that Salmonella infection among contacts (household members and nurses) occurs more frequently than present statistics indicate. The combined bacteriological and serologic approach to the diagnosis of salmonellosis may eventually yield more accurate information on the true incidence of this disease, its epidemiology, and its clinical manifestations.

RADIOLOGY

The Value of Arteriography in the Diagnosis of Bone Tumors. B. Strickland. Brit. J. Radiol. 32:705-713 (Nov.) 1959 [London].

Although percutaneous arteriography cannot replace a biopsy in the diagnosis of osseous tumors, it may assist in their diagnosis, differential diagnosis, and management. Pathological vessels are present in malignant tumors in a typical pattern. They appear as deploying without purpose, keeping to no set course, and showing no progressive diminution in caliber. As they run through the mass of the tumor, their walls may be lined with tumor cells, and remain filled with contrast medium for a considerable time, owing to the lack of residual elasticity. An abrupt termination of an otherwise normal artery in the neighborhood of a bone tumor is also a fairly frequent finding in malignant disease, probably due to local thrombosis or infarction in the tumor itself.

Twenty-seven patients with tumors of different types and etiology were studied by arteriography. In 10 patients the findings indicated absence of malignancy in neoplasms which from clinical and radiologic data appeared to be malignant. In 3 patients the diagnosis of malignancy was either confirmed or suggested. Further confirmation was found during surgical treatment. In 8 patients arteriography showed that the vessels are deeply affected by radiotherapy. In 3 of these patients the findings showed the persistence of a still abnormal vascular pattern; in the other 5 they indicated a return to a normal pattern. However, later developments or surgical exploration demonstrated that tumor cells were still present. This shows that arteriographic data cannot demonstrate the effectiveness of the radiotherapy, although the pattern is very definitely affected by x-rays.

The meaning of arteriographic findings is more difficult to interpret in relation to metastases. The vascular pattern in metastatic tumors is roughly proportional to the vascularity of the primary tumor, but the site of the primary growth cannot be deduced from the vascular pattern of the metastases. The author believes that arteriography should be requested as a routine investigation before deep x-ray therapy, for the purpose of defining the limits of the growth, which are often different from the appearances of the plain x-ray film.

"Toxic" Segmental Dilatation of the Colon During the Course of Fulminating Ulcerative Colitis: Roentgen Findings. B. S. Wolf and R. H. Marshak. Am. J. Roentgenol. 82:985-995 (Dec.) 1959 [Springfield, Ill.].

The authors report on 11 patients with fulminating ulcerative colitis, associated with severe intrinsic inflammatory disease of the colon wall and localized colonic dilatation. Pathologically, this condition is characterized by acute inflammatory changes in all coats of the colon with areas of necrosis; clinically, it is marked by extreme toxicity and high frequency of perforation. Roentgenologic changes can best be detected by simple roentgenogram. Barium enema examination is unnecessary and undesirable. Characteristic roentgenologic changes in patients with toxic segmental dilatation of the colon consist of (1) marked distention of one or several parts of the colon, (2) obliteration of the haustral and mucosal pattern, (3) irregular contour of the colon, with multiple deep projections indicative of ulceration, (4) numerous nodular pseudopolypoid intraluminal protrusions, (5) a lack of redundancy or a relative shortening of the colon, and (6) an inability of the colon to contract normally due to a loss of tone. Toxic segmental dilatation may develop within 3 or 4 days. Normal tone may be restored within a period of 1 or 2 weeks after the performance of a cecostomy. From the roentgenologic point of view, there must be considered differentiation from paralytic ileus or mechanical intestinal obstruction of the colon, from megacolon (Hirschsprung's disease), from "sentinel" dilatation during the course of acute pancreatitis, from markedly dilated loops of small intestine in ileojejunitis, and from marked colonic dilatation occasionally seen in sprue. None of these conditions show the remarkable localized colonic dilatation in association with severe intrinsic inflammatory disease of the colon wall.

Observations on the Small Bowel Pattern Associated With the Zollinger-Ellison Syndrome. J. M. Weber, S. Lewis and K. H. Heasley. Am. J. Roentgenol. 82:973-977 (Dec.) 1959 [Springfield, Ill.].

The authors describe the appearance of a small intestine pattern, as observed in 3 patients with the Zollinger-Ellison syndrome, and they suggest that the pattern may prove to be diagnostic or highly suggestive of the syndrome. Roentgenologic studies of the small intestine in these 3 patients revealed a distinctive lacy, cobweb-like pattern. It is believed that marked motor irritability associated with hypersecretion might be the possible mechanism producing the roentgenologic pattern, as well as the diarrhea which was a prominent symptom in the 3 patients. It is recommended that roentgenologic studies of the small intestine be performed in all those patients in whom the diagnosis of the Zollinger-Ellison syndrome is being considered. This includes patients with intractable diarrhea, even though peptic ulcer symptoms are not present.

The Incidence of Colonic Diverticulosis. C. C. Smith and W. R. Christensen. Am. J. Roentgenol. 82:996-999 (Dec.) 1959 [Springfield].

The authors reviewed 1,016 consecutive barium enema studies and analyzed the results to provide some indication of the actual incidence and distribution of diverticulosis. This group of patients is not the result of random population sampling, but it is rather typical of hospital and outpatient clinics where roentgenologic services are readily available. Under these circumstances, a low incidence of colonic disease is to be expected, and some resemblance to the general population is present. Of the 1,016 patients, 21.8% had diverticulosis; their average age was 70.4 years. No difference in incidence between male and female patients was noted. In half of the patients the abnormality involved a single segment, and in the other half more than one segment was affected. In 73% of the patients the descending and sigmoid areas were most frequently affected by diverticulosis. It is of interest that the older patients did not show a higher incidence of generalized disease than the younger. No obvious association with malignancy of the colon has been observed. Once manifested, the disease does not appear to be progressive.

BOOK REVIEWS

Fundamentals of Modern Allergy. Edited by Samuel J. Prigal, M.D. Sponsored by New York Allergy Society. Cloth. $18.50. Pp. 690, with illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E. C. 4, England; 253 Spadina Rd., Toronto 4, Canada, 1960.

This volume is a compilation of 63 essays written for and published in the *New York State Journal of Medicine*. Except for several guest writers, the authors of the papers are members of the New York Allergy Society. The readers for whom these essays were written required a brief, often superficial, statement of difficult problems in allergy. Such complex problems as atopic dermatitis, gastrointestinal allergy, and food allergy are each discussed in 5 to 13 pages.

The superficial content of most of the essays is only one objection to the book. Another is the absence of order in organization. The editor assumed the difficult task of trying to organize 63 brief essays by 51 authors into a textbook. The only evidence of organization is the grouping of the various essays in the following sections: (1) Mechanics and Causal Factors in Allergy, (2) Tests, Procedures, and Technics for Diagnosis of Allergic Conditions, (3) Manifestations and Forms of Allergy, (4) Allergy in Childhood and Old Age, and (5) General Treatment and Prophylaxis in Allergy. As individual papers published in a state medical journal, these contributions served a useful purpose. Their inclusion in one published volume fails to make the book either a textbook for the novice in allergy or a reference book for the trained allergist.

Diagnostic Radioisotopes. By Charles A. Owen, Jr., M.D., Ph.D., Associate Professor of Clinical Pathology, Mayo Foundation, Graduate School, University of Minnesota, Rochester. Cloth. $15.75. Pp. 425, with 71 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This volume, specifically limited to the diagnostic aspects of the use of radioisotopes in medicine, should be useful to many physicians interested in acquiring a survey knowledge of this field. It is particularly comprehensive in dealing with tests of thyroidal function and the applications of radioisotopes to hematological problems, the two fields which represent a major section of present diagnostic radioisotope use. In such a rapidly changing field as the development of radioisotopic procedures, the time lag between preparation of a book and its publication is particularly noticeable, and in this instance the latest references are from the literature of 1956. Important new developments such as the work of Pochin with the short half-life iodine-132 and the more recent chromium-51 sequestration studies are missing. Good organization, clear writing, and an excellent bibliography are noteworthy. There are 528 bibliographic references to thyroid studies alone.

The book is mainly clinically oriented. Only 55 pages are devoted to measurement methods, and these do not seem adequate to carry the beginner to the point of sufficient familiarity with instrumentation methods at which accurate and reproducible results might be expected. The treatment of radiation protection is casual, and while the hazards in the use of diagnostic quantities of radioisotopes are small they are of sufficient importance to merit more than passing reference. In conjunction with other textbooks and the more recent literature, this volume is a worthwhile addition to the library of physicians who wish to become more familiar with the diagnostic applications of radioisotopes in clinical medicine.

Biophysical Science: A Study Program. Planned and edited by J. L. Oncley, editor-in-chief, and others for Biophysics and Biophysical Chemistry Study Section of National Institutes of Health, Public Health Service, United States Department of Health, Education, and Welfare. Published in Reviews of Modern Physics, January and April, 1959. Cloth. $6.50. Pp. 568; 27, with illustrations. John Wiley & Sons, Inc., 440 Fourth Ave., New York 16, 1959.

This collection of 61 papers is based on the study program held in Boulder, Colorado, in the summer of 1958. These papers cover a wide range of subjects, including molecular biology and the physical basis of life processes; molecular configuration of synthetic and biological polymers; physicochemical characterization of macromolecules; proteins and their interactions; mechanisms of enzyme action; coding and information theory; radiation inactivation of enzymes, nucleic acids, and bacteriophages; membrane transport; nature of the nerve impulse; sensory performance of organisms; and hormone regulation.

They are summaries of present knowledge as well as carefully documented excursions into the more basic physical and chemical foundations of important biological phenomena. Several are of particular and current interest to the physician. In his paper, "Hormone Regulation," Stetten has summarized our present knowledge of the chemical structure of insulin, glucagon, and the hormones of the posterior pituitary gland. He has explained the effects of these hormones in terms of enzymatic and other cellular mechanisms, for example, the role of insulin in the diabetic organism in increasing the permeability of the muscle cell to glucose and in reversing the increased activity of glucose-6-phosphatase. In his paper, "Blood Coagulation—A Study in Homeostasis," Waugh had surveyed the various components and factors involved in this process, the way in which they interact, and the aspects which need future study. The isolation and purification of enzymes which carry out the synthesis of ribonucleic and desoxyribonucleic acids have been of outstanding interest in the past few years. These and related recent advances in this important and crucial field are reviewed by Kornberg in "Biosynthesis of Nucleic Acids."

The content of many of the papers may appear quite remote from the concerns of everyday medical practice, but as the history of progress in medicine and other sciences has shown, there is an unceasing and dynamic flow of theory into practice. The present volume is highly recommended to the clinical investigator as an authoritative survey of rapidly expanding fields which may, in one way or another, affect his own research. This book should benefit physicians who are curious about the chemical and physical foundations of biology and who wish to obtain a glimpse of the matrix of medical knowledge in the forseeable future.

Measurement of Subjective Responses: Quantitative Effects of Drugs. By Henry K. Beecher, M.D., Henry Isaiah Dorr Professor of Research in Anæsthesia, Harvard University, Boston. Cloth. $12.75. Pp. 494. Oxford University Press, 417 Fifth Ave., New York 16, 1959.

This book is an expansion in depth as well as in length of a review on the measurement of pain published in *Pharmacological Reviews* several years ago. In the present volume, Dr. Beecher has explored the difficult and complex field of measurement of subjective responses and has produced an interesting and provocative book. He has revised the section on methods for the evaluation of pain and discusses the characterization and measurement of such phenomena as mental clouding, sedation, euphoria, dysphoria, nausea, hunger, anxiety, itching, and the subjective and objective components of cough. A discussion of placebo reactors, psychotomimetic drugs, and the quantitative effects of anesthetic substances on subjective state is also included. Since the author is a pioneer in the field of measurement of subjective response, it is not surprising that much of the work reviewed is either from his laboratory or from the laboratories of investigators who were trained in his methods at the Massachusetts General Hospital.

The major criticism of the book is that its approach still has the savor of a review and does not really provide a unifying concept of the field of quantification of subjective responses. Perhaps this is all that is possible in view of the present state of knowledge in this field. Dr. Beecher has written a useful and stimulating book which should be of interest to workers in the behavorial sciences, to pharmacologists, to all who work with the evaluation of drugs affecting subjective states, and to those who are dissatisfied with clinical impressions alone as a measure of drug activity in man. Research workers in fields where experimental design is critical would do well to read it and reflect on some of the problems it poses. A comprehensive bibliography further enhances its value.

Complete Child Care in Body and Mind: A Modern Parents' Guide to the Healthy Growth and Development of the Newborn, the Infant, the Child and the Adolescent. By I. Newton Kugelmass, M.D., Ph.D., Sc.D. Cloth. $6.95. Pp. 415. Twayne Publishers, Inc., 31 Union Sq. W., New York 3, 1959.

This fact-packed volume contains the story of childhood health care from birth through adolescence. It is a plain book with no fancy art work, no glossy prints, no color plates, and no typographical embellishments. It is perhaps best described as a working book, into which the author has put a world of information. Since the author is no amateur in this area, he has arranged his material in an attractive and logical manner. The volume is divided into five parts, dealing with the infant, the preschool child, the school child, the preadolescent, and the adolescent. These parts contain detailed discussions that clarify the many questions which inevitably occur to all parents.

There are 28 tables in the book, most of which present detailed information about feeding schedules, menus, and choice of special-purpose foods. There are height-weight charts, information about caloric values of common foods, and two interesting tabulations dealing with identification of various stages of personality development and graduation from immature to mature attitudes. As the author suggests, the volume should be of much interest and assistance to parents, nurses, and teachers since it considers child development against the background of newer information regarding physical and psychological needs in all growth periods. An extensive index adds to practical usefulness of the book.

Proceedings of the World Congress of Gastroenterology and the Fifty-ninth Annual Meeting of the American Gastroenterological Association, Washington, D. C., U. S. A., May 25th through 31st, 1958. Volumes I and II. Cloth. $20. Pp. 714; 715-1363, with illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2, 1959.

The great number of authoritative participants in the Congress here reported made it possible to develop two types of presentation: symposiums dealing with topics of great importance and world-wide interest and original contributions of basic scientific and clinical value. One symposium covered the epidemiologic and clinical features of peptic ulcer throughout the world with panel discussions and summarized conclusions on the total presentations. There were symposiums on the malabsorption syndrome, nutrition and its effects of the liver and pancreas, intestinal infections and infestations, and the education of the gastroenterologist with particular emphasis on the future of the field of gastroenterology. Original contributions covered gastrointestinal physiology, intestinal infections and infestations, affections of the pancreas and biliary tract, peptic ulcer from the standpoint of etiology and epidemiology, intestinal malabsorption, nutritional and physical aspects of affections of the liver and pancreas, upper gastrointestinal hemorrhage, pathological and clinical features of affections of the intestines, gastric carcinoma, and gastric surgery.

These proceedings, which in many instances point out the geographical, racial, and national differences in epidemiology and in clinical behavior patterns of disease, are highly significant and may become a standard reference work. Anyone interested in any phase of gastroenterology and nutrition cannot afford to be without them.

Pyelonephritis. By Fletcher H. Colby, M.D. Cloth. $7.50. Pp. 214, with 95 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2, 1959.

In this book the relations of pyelonephritis to uremia, obstructive uropathy, diabetes, pregnancy, and hypertension are illustrated by case histories. The forms encountered in infancy and childhood and the evolution from acute or latent subclinical disease are fully discussed. The literature and history of knowledge of pyelonephritis are also given. This is a brief but well-balanced monograph by a careful observer with great experience in the field. His discussion of therapy and his discouraging report on the value of antibiotics in the chronic or subacute disorder should be read by every internist and pediatrician. The techniques for identifying unilateral disease as a possible cause of hypertension and the way in which diabetes, hypertension, and proteinuria predispose the kidney to hematogenous infection are not stressed. However, these are of more concern to specialists and pathologists than to the larger group for which this book was written.

Angiologie Pathologie, Klinik und Therapie der peripheren Durchblutungsstörungen. Herausgegeben von Prof. Dr. Max Ratschow, F.A.C.A. Unter Mitarbeit von W. Block et al. Cloth. 174 marks; $41.45. Pp. 831, with 373 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

This massive volume is a typical example of Germanic thoroughness, of systematic treatment of an enormous literature, and of great pride in national accomplishment. Some of the chapters written by preclinical scientists are of the highest order. Many of the clinical chapters are belated statements of American and British work with little originality and much generalization. The production of the book, including paper, printing, and illustrations, is excellent. It is an example of the rapid recovery Germany has made in the technical field. It is doubtful, however, that the American reader would benefit much from reading this "hypertrophic" textbook. It furnishes a lucid account of vascular allergies and still advocates use of fresh calf pituitary implants in persons with Raynaud's disease. A final short chapter on the aspects of vascular disease as it relates to the state insurance system is highly revealing. Endless litigation and conflicting testimony of experts is reminiscent of some of the files confronting the compensation boards of the Veterans Administration.

Rheumatic Fever: Epidemiology and Prevention. The Proceedings of a Seminar held at the International Children's Centre, Paris, 25-27 September 1956. Editors: R. Cruickshank, M.D., Ch.B., F.R.C.P., and A. A. Glynn, M.D., B.S., M.R.C.P. Cloth. $5.50. Pp. 193, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This symposium was first published in French. The material is covered in four parts: (1) the biology of group A hemolytic streptococci, (2) the epidemiology of infection with group A hemolytic streptococci, (3) the epidemiology of rheumatic fever, and (4) the prevention of rheumatic fever. Neither the diagnosis nor the treatment of rheumatic fever were dealt with at this conference. The papers are well illustrated, comprehensive references are listed, and the material is presented cohesively. The editors have accomplished their goal in presenting the English version of the conference. The monograph should serve a useful purpose for those interested in the epidemiology and prevention of rheumatic fever.

Diseases of the Nose, Throat and Ear: A Handbook for Students and Practitioners. By I. Simpson Hall, M.B., Ch.B., F.R.C.P.E., Surgeon to Royal Infirmary, Edinburgh. Seventh edition. Cloth. $5. Pp. 467, with illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2; E. & S. Livingstone, Ltd., 16 and 17 Teviot Pl., Edinburgh 1, Scotland, 1959.

This handbook was conceived primarily for the use of students and practitioners. It is written from the experience of its author, a fact which is responsible for its many virtues and perhaps for some of its limitations. Because of its intended audience and its self-imposed restrictions, much detail is omitted, primarily in the field of operative procedure. This is altogether proper. It is for these reasons and for its general high tone of excellence that this work may be highly recommended to those for whom it was written.

QUESTIONS AND ANSWERS

THREATENED ABORTION

To the Editor:—*Would you summarize the treatment for threatened abortion? What management is best for the woman who repeatedly aborts in the early stage of pregnancy? What is the role of the new synthetic progestational hormones?* M.D., Wisconsin.

Answer.—The term threatened abortion is ill-defined, for it is often applied to all women having vaginal bleeding in the early weeks of pregnancy, which has authoritatively been stated to occur in 20 to 25% of all pregnancies. Since only 8 to 10% of women abort, vaginal bleeding per se is not synonymous with a threatened abortion. It is evident that the chance of a cure for women with the single sign of vaginal bleeding, without therapy, is 50% or more, a fact to be kept in mind when assessing the value of the various forms of therapy.

Common sense dictates bed rest for a few days for patients confronted with so-called threatened abortion, but it is questionable whether other therapy is required or indicated. Since it is believed that the conceptus is rarely normal when the abortion occurs by the 10th or the 12th week, it is doubtful that any form of therapy is indicated once bleeding occurs in the patient destined to abort in the first trimester. The abortion is presumably the result of a germ plasm defect or of faulty implantation.

To be most effective, treatment of the woman who has had repeated abortions should begin prior to conception and be directed toward improvement of the general health of the patient and of the blood supply to the future implantation site. To achieve the latter, the administration of small amounts of progesterone or diethylstilbestrol during the secretory phase of the cycle has been advocated. Although sex reversal of the fetus has followed sex steroid therapy, the incidence is extremely low. This condition is temporary and thus reversible, and it is most likely to occur from the administration of progesterone-like compounds with an androgenic component. The latter is lacking in some compounds, however, and such progesterone-like synthetic substances without an androgenic effect, or progesterone itself, should be considered part of the therapy.

Women who lose the conceptus after the first trimester and before the period of medical viability may have incompetent cervixes. The inquirer is referred to published papers for consideration of this difficulty.

In summary, in the so-called chronic aborter, the time at which the conceptus has been lost should be established, and whether it is anatomically normal or abnormal. If the abortion occurs in the first trimester, preconceptional treatment as outlined is indicated. In those who abort later, the major item in the treatment includes copious amounts of rest and sex-steroid therapy, and the question of surgery for the incompetent cervix should be considered. Considerable credence has been given to the value of psychotherapy, but this should be within the capabilities of any well-informed and understanding physician.

Until more is known of the fundamental biology of the factors which control the reproductive cycle the treatment of premature loss of pregnancy, including the various types of abortion, must remain empirical. This permits marked differences of opinion regarding preferred forms of treatment.

LOSS OF HEARING IN CHILDREN

To the Editor:—*What would cause a progressive loss of hearing in a 3½-year-old girl? Her general physical health is normal. Her tonsils and adenoids are not enlarged, and the light reflex from both tympanic membranes is normal. The loss of hearing is apparently not secondary to other causes. The child is right-handed and her visual orientation is normal. She has difficulty in understanding what is being said and in obeying simple commands given in conversational tones but responds to a loud voice at close range. She herself speaks quietly and frequently whispers; her speech is slurred to the point of unintelligibility. In a sound-field test she consistently responds both to the spoken word and to noise signals at levels between 40 and 60 db. of normal.*

J. Philip Fox, M.D., Cincinnati.

Answer.—The diagnosis of impairments of hearing in children of preschool ages is difficult because of their inability to communicate normally and their related handicap in performing formal tests.

In "Auditory Disorders in Children" (New York, Grune & Stratton, Inc., 1954) Professor Myklebust describes four possible causes of delayed acquisition of speech in a child. The most common cause, occurring in 50%, is a severe impairment of hearing, which usually is congenital. If the impairment does

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

not exceed 40 or 50 db. in the frequencies of normal conversational tones, the child will learn to talk at nearly the normal rate. The greater the impairment of hearing, the longer the delay in acquisition of speech, and, when the loss of hearing exceeds 70 or 80 db., the child cannot learn to talk without special training. Often the parents are not aware of their child's loss of hearing until they notice his delay in learning to talk. A mild or moderate impairment in hearing may be present from birth but may not become apparent until the child is 3 or 4 years of age. The parents then assume that there is a progressive loss, when actually the *hearing is at a stable level.*

The second most frequent cause for delayed acquisition of speech is brain damage, presumably incurred at birth, which affects the speech centers and produces aphasia. These children's responses to sound are inconsistent, and other evidences of brain damage will be present. The third cause for delayed acquisition of speech is mental retardation or feeblemindedness, and the fourth is an emotional disturbance of an infantile autistic type.

In the child described, the difficulty is likely to be caused by more than a mere impairment in hearing, and a psychoneurological study is indicated. She apparently had normal auditory function at one time, which suggests the possibility of progressive nerve deterioration. The latter is a rare condition which occurs on a familial basis.

CONVERSION OF TUBERCULIN SKIN TEST

To the Editor:—*Does current scientific opinion hold that patients who are PPD (purified protein derivative) converters (those who, having had a negative reaction one year previously, show a positive reaction to a skin test with purified protein derivative of Mycobacterium tuberculosis) should receive treatment if they have no other clinical or roentgenologic signs of active tuberculosis?* *M.D., Arizona.*

Answer.—The conversion from a negative to a positive reaction to the tuberculin skin test usually means that the patient has had a recent infection with tubercle bacilli. There are other situations in which conversion from a negative to a positive reaction actually occurs or seems apparent, but they are of purely academic interest and need not be discussed here.

Clinicians differ in their opinions about the proper management of patients who are first-infection "converters." Current research projects are attempting to solve this problem but have not as yet brought forth a consistent or wholly acceptable approach. Some phthisiologists believe that no treatment need be given unless the patient has demonstrable lesions or presents clinical signs of the disease. This has been the method used in the past, and, under good medical observation, it is still entirely acceptable. Some physicians advocate treatment for prophylactic reasons, since fulminating manifestations of tuberculosis may develop in this type of patient. Other physicians treat all converters radically, irrespective of the clinical and roentgenographic findings, especially those who have strongly positive tuberculin reactions. The number of physicians who believe that all converters should be treated is increasing, and practically all agree that children under 2 years of age should receive treatment with isoniazid for one year or until the tuberculin reaction has disappeared.

It is clear that there is as yet no uniform opinion about age groups to be treated. A fair composite plan for those patients who have a converted reaction would be to treat every child under 3 years of age, irrespective of the magnitude of the reaction; other children and adults with positive (3 to 4+) reactions should be treated with isoniazid for at least one year. Their progress should then be followed for one to two years by means of roentgenographic study and clinical observation.

IRRIGATION OF THE EAR CANAL

To the Editor:—*Is it possible for water to remain on the tympanic membrane and give the patient a feeling of blockage after removal of wax from the ear canal by the irrigation method?* *M.D., Rhode Island.*

Answer.—It is possible for water remaining on the tympanic membrane to give the patient a feeling of blockage for a short length of time, but if the drum is wiped with a cotton applicator this sensation usually disappears. If the drum is not wiped dry, the feeling of fulness may persist for an hour or two. If it persists longer than this, it can mean that some other condition is present, such as edema of the tympanic membrane due to irritation by a foreign body. One must rule out other possibilities such as slight loss of hearing.

CEREBRAL PALSY AND CESAREAN SECTION

To the Editor:—*What percentage of persons with cerebral palsy are delivered by cesarean section, and how does this number compare with the percentage of cesarean sections performed in the United States?* *Kurt Schnitzer, M.D., Santa Ana, Calif.*

Answer.—Eastman and Kohl, in the last two years, did a retrospective study of cerebral palsy. Of 383 patients with brain damage, 10 infants, or 2.6%, were delivered by cesarean section. In a control series of 364 infants (each now normal and healthy), 7, or 1.9%, were delivered by cesarean section. Eastman's and Kohl's figures on the total number of cesarean sections performed are 3% in the control group of women and 4.2% in that of women with cerebral palsy.

These figures of 3 and 4.2%, respectively, probably have little significance, for they include cesarean sections performed on women having abruptio placentae, placenta previa, preeclampsia, diabetes, and other conditions which might affect the health of the baby. The investigators were unable to demonstrate that elective cesarean section performed before the onset of labor reduces the incidence of cerebral palsy by elimination of the trauma caused by mechanical forces during the second stage of labor.

VENIPUNCTURE TECHNIQUE

To the Editor:—*After performance of a venipuncture in the area of the antecubital space, it is common practice to place a sterile cotton ball over the vein and instruct the patient to flex his arm. It has been suggested that this procedure be changed to application of direct pressure with a sterile cotton ball to the site of the venipuncture while the patient elevates and extends his arm to minimize the extravasation of blood. Which method is better?*

M.D., New York.

Answer.—While the needle is being withdrawn, a pad of wool or gauze should be pressed on the site of venipuncture, and the patient should be instructed to keep his arm straight and to raise it. Pressure should be maintained on the pad by the patient or some one else. The practice of retaining the pad in position by flexing the elbow is less satisfactory; not only is less pressure brought to bear on the vein at the site of puncture, but pressure may actually be applied proximal to the site of puncture and thus promote bleeding. (Mollison, P. L.: Blood Transfusion in Clinical Medicine, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1957, p. 4.)

ALLERGY TO ARTIFICIAL EYE

To the Editor:—*What is the incidence of allergic reaction to a plastic implant in the orbit? A patient on whom an eye enucleation and evisceration has been performed is wearing a plastic artificial eye made of methyl methacrylate. It is claimed that the vision in the remaining eye is affected because of an allergic reaction to the artificial one, although there has been no evidence of inflammation. How often does this condition occur, and what other plastics can be used?*

M.D., New York.

Answer.—Allergic reactions have been reported to methyl methacrylate in dental prostheses and in artificial fingernails. Macivor (*Canad. M. A. J.* 62:164 [Feb.] 1950) reviewed 100 patients with plastic prostheses; 8 had a contact allergy, 6 from artificial eyes and 2 from partially exposed implants. The artificial eyes were composed of methyl methacrylate. Practically all plastic orbital implants on the market are made of plastics that are polymers of methyl methacrylate.

The patient should have a patch test with the liquid monomer or powdered polymer of the suspected plastic. Substitution of a glass or gold implant, however, would probably be the most direct method of management.

No effect is likely to occur in the remaining eye, provided all uveal tissue was removed at the time of operation.

BAN ON SMOKING IN GYMNASIUMS

To the Editor:—*What scientific study could be used as a reference for the ban on smoking in a basketball area or a gymnasium?*

Frank Vinson, M.D., Fort Valley, Ga.

Answer.—A suitable reference is the study by Karpovich and Hale, entitled "Tobacco Smoking and Athletic Performance" (*J. Appl. Physiol.* 3:616 [April] 1951).

RETROBULBAR NEURITIS AND PREGNANCY

To the Editor:—*A woman had retrobulbar neuritis of the left eye when she was 16 years of age. Since then she has been well, except for an episode of retrobulbar neuritis in her right eye, which gradually cleared, one month after her second pregnancy; neurological findings were normal. What advice should one give this patient with regard to future pregnancies?*

Harold C. Blog, M.D., Huntington, N.Y.

Answer.—Since no etiological diagnosis of the retrobulbar inflammation has been made in this patient, no specific answer can be given. Assuming that diagnostic studies have been performed, and that the patient does not have any progressive type of vascular, inflammatory, or neoplastic lesion, only a general consideration of her problem can be given.

Quantitative perimetry, roentgenographic studies of the skull and optic foramen, electroencephalography and studies of spinal fluid dynamics and chemistry should be carried out. Remote causes of retrobulbar neuritis such as diabetes, alcohol and tobacco amblyopia, lead or lead-salt poisoning, and the like should be excluded. Retrobulbar neuritis commonly occurs in women under 35 years of age, and, since this is the maximal child-bearing period, the occurrence of this disease one month after the second pregnancy does not indicate a causal relationship between pregnancy and the disease. Moreover, this patient had an attack at the age of 16 years when she presumably was not pregnant, and she has had two pregnancies without developing signs of the disease; the condition recurred only after termination of the second pregnancy. Although there are reports in the literature that pregnancy can be responsible for the onset of retrobulbar neuritis, this relationship must be studied and established before it can be applied to the individual patient.

CEPHALALGIA

To the Editor:—*A 40-year-old housewife has complained of cephalalgia for 18 months. Neurosurgeons have performed neurectomies of the greater and lesser occipital areas, with severance of all nerves in the right inferior portion of the head. She had obtained temporary relief from pain and now experiences an intermittent, burning, dull ache along the maxillary division of the trigeminal nerve and pain in the region of both mastoid processes. Since the patient has a great degree of psychic overlay, administration of tranquilizers has been of some benefit. Various analgesics, including tablets containing salts of dihydrohydroxycodeinone and homatropine plus acetylsalicylic acid, acetophenetidin, and caffeine citrate (Percodan); tablets containing ethoheptazine citrate and acetylsalicylic acid (Zactirin); and, at one time, anileridine (Leritine) dihydrochloride, have been used. A series of vitamin B^{12} injections has also been prescribed. What suggestions can be given for alleviation of the pain?*

Bruce C. McIntyre, M.D., Whitefish, Mont.

Answer.—In 1947, Gardner and co-workers undertook treatment of patients with unilateral head pain by division of the greater superficial petrosal branch of the seventh cranial nerve. The rationale of their procedure stemmed from the collaborative work of Cobb and Finesinger with Chorobski and Penfield, who had shown that this nerve contains secretory fibers for the lacrimal glands, vasodilator fibers for the mucous membranes of the nasal cavity, and afferent fibers, from the dura mater, the internal carotid artery, and the sphenopalatine ganglion, to the cells in the geniculate ganglion and that it conveys vasodilator impulses to the ipsilateral cerebral hemispheres. Gardner and associates, inferring that parasympathetic impulses transmitted by the petrosal nerve caused unilateral lacrimation, unilateral swelling, secretion of the nasal mucosa, and unilateral head pain, sectioned this nerve in 26 patients with unilateral cephalalgia. While in about one-third of the patients the headache was eliminated immediately after the operation, in another third there was only some diminution of pain, and in the remaining third none at all. The pain of unilateral cephalalgia has not been significantly reduced or eliminated by division of the fifth or ninth cranial nerves, and, with the exception of patients with cranial or temporal arteritis, surgical resection of nerves or arteries in the head has not proved to be of therapeutic value for vascular headaches. It is also well known that headaches, after management by such other therapeutic procedures as desensitization to histamine, recur in these patients in situations of tension, desperation, or exhaustion. Mood reactions in these patients, which are characterized by long-standing resentment, hostility, and anger, precede and persist in the interval between attacks. The administration of ergotamine tartrate will successfully abort many individual attacks of cephalalgia, but no medication can be expected to prevent the recurrence of attacks. It is necessary to insist that these patients follow through with a detailed regimen of work and recreation that brings them satisfaction and permits them to have adequate periods of rest and to prescribe measures to induce relaxation such as massage, long, warm tub baths two or three times a day, exercise, and small amounts of a sedative or analgesic agent. Most important is the direction of therapeutic attention at the patients' destructive attitudes and moods, and the life situations in which they occur, that precipitate the attack. Headaches can be effectively modified in most patients by these measures.

VENOCLYSIS AND THROMBOPHLEBITIS

To the Editor:—*What is the incidence of thrombophlebitis after injection of a 50% dextrose solution into a patient's antecubital vein? What is the incidence if a 5% dextrose solution is used?*

H. James Byrne, M.D., Glendale, Calif.

Answer.—Etiological factors which are not specific but are contributory in causing thrombophlebitis include the rubber or plastic tubing equipment, the tonicity and pH of the infusion fluid, and the duration of the infusion. The incidence of thrombophlebitis as a result of infusion can be reduced by (1) a change in the site of the venipuncture every eight hours, and (2) injection of irritant solutions into a large blood vessel in which they will be diluted rapidly. A 50% dextrose solution should be infused through a plastic tube that has been passed up a brachial vein to its junction with the subclavian (Mollison, P. L.: Blood Transfusion in Clinical Medicine, ed. 2, Springfield, Ill. Charles C Thomas, Publisher, 1956, pp. 425-426). The incidence of thrombosis after injection of a 5% dextrose solution into an antecubital vein is negligible, according to the experience of a transfusion unit in a large midwestern hospital. Most of the complications arise when drugs are added to the solution. Tabulation of the incidence of thrombophlebitis due to infusion of a 50% dextrose solution has not, apparently, been done.

Dr. Robert Helig Library

Administration Attacks Forand Scheme . .
Key GOP Lawmakers Agree . .
Aid for Medical Schools . .
U. S. Medical Research Role . .

ADMINISTRATION RENEWS OPPOSITION TO FORAND APPROACH

A significant development in the controversy over government medicine schemes was the decision by the Eisenhower administration not to propose at this time any alternate to the controversial Forand bill.

Equally important, the administration emphatically renewed its opposition to any type of proposal such as Forand's to broaden the social security mechanism by providing partial financing of medical and hospital bills for some of the aged population.

The administration's stand was revealed by Arthur S. Flemming, Secretary of Health, Education, and Welfare, in testimony before the House Ways and Means Committee that was considering the Forand bill and other changes in the social security program. "I want to make it clear," he said, "that as an administration we will oppose any program of compulsory health insurance."

Opponents of plans to inject the federal government further into the medical and hospital field had feared that any administration "alternative" during this election year would only have spurred Forand bill backers to push their own plan.

There had been indications earlier this year that the administration might offer the Ways and Means Committee at its sessions on social security some program in the field of health care for old persons. However, President Eisenhower decided against this.

While the administration's position was a heartening development as far as the medical profession was concerned, it by no means signaled the end of the matter in Congress. Rep. Aime Forand (D., R. I.) second-ranking Democrat on the Ways and Means Committee and sponsor of the disputed health-care-for-the-elderly bill, filed a discharge petition to try to bypass the Committee and bring the measure up on the House floor for a vote.

Forand apparently took the action because of a belief that a majority of the Committee was opposed to his measure. The discharge petition is a seldom-used maneuver aimed at having the full House take up legislation without the usual necessity of Committee approval. To succeed, a majority of the House membership—219 members—must sign the petition.

In his testimony, HEW Secretary Flemming did not write off the possibility that at some later date the administration might come up with an alternate program. Stating that further consultations would be held with experts in the field, Flemming said, "It is . . . not possible to predict the length of time that it will take for these consultations.

"Moreover, I am not now in a position to predict how long it will take to resolve the basic issues . . .," he added.

Even if an alternative administration program is developed before this session of Congress adjourns, probably sometime in July, in all likelihood it would be too late for Congressional action this year.

Noting that last year he had testified that, under the Forand bill, "The pattern of health coverage of the aged would be frozen in a vast and uniform governmental system," Flemming told the Committee that in view of progress made by free-enterprise, voluntary means, "We are all the more convinced that it would be very unwise for our government to take any step that would lead to such a result."

Listing his objections to the Forand measure, Flemming noted "very significant steps that the federal government has taken in recent years to help deal with hazards of old age." These included increases in payments to social security beneficiaries, stepped-up medical research programs, funds for hospital construction, and special housing projects for the elderly.

Furthermore, the cabinet officer pointed out, Congress has provided for a White House Conference next January on all aspects of aging problems.

"Very significant advances" have been made in recent years in extending the benefits of health insurance to people 65 years of age and over, Flemming testified, with about 42% of persons in this age group now covered by some protection against the cost of hospital care. And private companies are aggressively entering the field to provide better protection for older persons, he added.

At the same time, Flemming said, "there still will be aged persons who will have no protection but would be willing to participate in voluntary programs if provided with policies at rates they could afford to pay." The administration has been investigating the feasibility of a program "that would help accelerate rather than impede the present voluntary approach to this problem," Flemming said.

In considering a program, the following principles were being kept in mind, according to the secretary: no compulsion; nothing to stifle private initiative; strengthen and stimulate the existing private system; preserve and strengthen the private relationships which now characterize the rendering of health services; opportunity for all aged to participate; and availability to the aged—particularly in the low income groups—of protection against catastrophic and long-term illnesses.

One plan under consideration, he disclosed, would involve federal payments to help the states provide the difference between the amount paid by policy holders in low income groups and the actual cost of the policy. "In exploring this question, we are keeping in mind the fact that the states would be authorized to contract with private groups for the insurance."

In other testimony, Flemming officially backed the main provisions of another bill before the Committee that would liberalize the social security program for the totally and permanently disabled. The

(Continued on next page)

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Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

major provision of this bill would remove the present requirement that a beneficiary be at least 50 years of age before receiving payments. Instead, there would be no age limitation.

Flemming also proposed that social security coverage be extended to self-employed physicians, a move opposed by the American Medical Association.

REPUBLICAN GROUP ASSAILS FORAND LEGISLATION

The 10 Republican members of the House Ways and Means Committee joined in a unanimous attack on the Forand measure as an unsound approach to the problems of the aging.

Displaying solid-front opposition to the principle of tacking health care programs onto the social security mechanism, the GOP lawmakers concurred in the statement of HEW Secretary Flemming criticizing the Forand measure.

"Our opposition to the Forand bill does not preclude our genuine interest in contributing to the solution of the problems of the aged," the lawmakers stated. "Many federal programs are already in operation to alleviate these problems. We join . . . in supporting a program of thorough and effective study toward finding answers to the health problems confronting our society."

The Republicans listed four major points in criticizing the controversial Forand bill:

1. It is discriminatory because it excludes, among others, 4 million aged who through no fault of their own do not have social security protection, as well as "the millions of Americans in the working force along with their families who may have just as urgent medical-economic problems as the aged."
2. It is unsoundly financed . . . the proposed social security tax increase would not cover the cost of such a program.
3. It disregards the progress that has been made in recent years by the medical profession and the insurance industry to provide health care to the aged.
4. It would preempt the work now in progress for the White House Conference on the Aging next year.

The Republicans signing the document were Representatives Noah M. Mason (Ill.), John W. Byrnes (Wis.), Howard H. Baker (Tenn.), Thomas B. Curtis (Mo.), Victor A. Knox (Mich.), James B. Utt (Calif.), Jackson E. Betts (Ohio), Bruce Alger (Texas), Albert H. Bosch (N. Y.), and John A. Lafore (Pa.).

ADMINISTRATION WEIGHS MEDICAL SCHOOL AID PLAN

A program to furnish federal aid for the construction of medical schools was under top-level administration consideration. U. S. Public Health Service Surgeon General Leroy Burney told Congress that "there is under consideration by the administration, without any action up to the present time at least, proposed legislation which would provide grants for the construction of teaching facilities for medical schools, dental schools, schools of osteopathy, and schools of public health."

Last fall, a special consultant group on medical education, appointed by the U. S. Public Health Service, recommended in a lengthy report illion-dollar, 10-year program of federal match- grants to help construct 20 to 24 new medical schools and expand existing ones.

Dr. Burney told a House appropriations subcommittee that this report "has received very wide interest and study and I think has done a great deal to alert not only the professional groups but the public in general as to the very, very urgent problem of health manpower."

Arthur S. Flemming, Secretary of Health, Education, and Welfare, told the same subcommittee, "We have got the obligation of developing an action program designed to take care of the problem." Pressed about specifics, he said he was "not yet crossing the bridge as to what should be the role of the federal government in dealing with it."

The American Medical Association has endorsed the principle of a temporary program of federal aid to help build new medical schools.

CAUTIONS AGAINST TOO MUCH FEDERAL MEDICAL RESEARCH

Secretary of Health, Education, and Welfare Arthur S. Flemming said it would be a "sad day" if the federal government ever financed most of the medical research in this country.

He told Congress that in his travels about the country he was often asked why individual persons should contribute to private charities such as the Heart Association and the Cancer Society in view of the amount that the federal government is putting up for this purpose.

"First of all, I point out that these groups are doing things other than research," Flemming told a House appropriations subcommittee. "I mean that they are engaged in the actual rendering of service. That is one reason why people should continue to give."

"The second thing that I point out is that in my judgment these organizations ought to continue to get money for research so we will never reach the point where the federal government will be putting up 80 or 90% for research. That will be a sad day for medical research."

MISCELLANY

Congress was asked by the administration to make it a federal crime to assault or otherwise interfere with Food and Drug Administration inspectors and other agents of the Department of Health, Education, and Welfare while they are officially engaged in their work. Such a law now applies to the Justice Department employees and certain other federal enforcement branches.

The Senate Finance Committee approved legislation authorizing taxpayers a full deduction on federal income tax for medical expenses paid for dependent parents 65 years or older. At present there are limitations on such deductions by those with dependent parents. Persons aged over 65 years who are not dependent under current law are entitled to full deductions for medical expenses.

Legislation to set up clinics to treat narcotics addicts and give them limited quantities of drugs was introduced by Rep. Victor Anfuso (R., N. Y.). Under the bill, the federal government would provide up to 5 million dollars in grants to the states to help them set up the out-patient clinics.

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MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.
1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 2.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-Dec. 1.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 25-30.

AMERICAN

1960

March

American Gastroenterological Association, Roosevelt Hotel, New Orleans, Mar. 31-Apr. 2. Dr. Wade Volwiler, Dept. of Med., Univ. of Washington, Seattle, Secretary.

Neurosurgical Society of America, Del Monte Lodge, Calif., Mar. 30-Apr. 2. Dr. Raymond K. Thompson, 803 Cathedral St., Baltimore 1, Secretary.

April

Alabama, Medical Association of the State of, Admiral Semmes Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery 4, Executive Secretary.

American Academy of Neurology, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

American Academy of Pediatrics, Atlantic City, Chalfonte-Haddon Hall, Apr. 20-22. Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill., Executive Director.

American Association for the Advancement of Science, Section on Medical Sciences, Vanderbilt University, Apr. 18-19. Dr. George R. Meneely, Vanderbilt University School of Medicine, Nashville 5, Tenn., Chairman.

American Association of Anatomists, Statler-Hilton, New York City, Apr. 11-16. Dr. Louis B. Flexner, Dept. of Anatomy, School of Medicine, Univ. of Pa., Philadelphia 4, Secretary-Treasurer.

American Association of Immunologists, Chicago, Apr. 11-15. Dr. Calderon Howe, Columbia Univ. College of Physicians and Surgeons, New York 22, Secretary-Treasurer.

American Association of Pathologists and Bacteriologists, Hotel Peabody, Memphis, Tenn., Apr. 28-30. Dr. Russell L. Holman, Dept. of Pathology, L. S. U. School of Medicine, New Orleans, La., Secretary.

American Association of Railway Surgeons, Drake Hotel, Chicago, Apr. 7-9. Mr. Chester C. Guy, 5800 Stony Island Ave., Chicago 37, Executive Secretary.

American College Health Association, Toronto, Canada, Apr. 27-30. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary Treasurer.

American College of Obstetricians and Gynecologists, Netherland Hilton Hotel, Cincinnati, Apr. 2-6. Mr. Donald F. Richardson, 79 W. Monroe St., Chicago 3, Executive Secretary.

American College of Physicians, Mark Hopkins & Fairmont, San Francisco, Apr. 4-9. Dr. Edward C. Rosenow Jr., 4200 Pine St., Philadelphia 4, Executive Director.

American College of Surgeons, Sectional Meeting, Hotel Leamington, Minneapolis, Apr. 11-13. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Kahler Hotel, Rochester, Minn., Apr. 14. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, West Virginia Chapter, The Greenbrier, White Sulphur Springs, W. Va., Apr. 1-2. Dr. Ray E. Burger, Grace Hospital, Welch, W. Va., Vice-President.

American Dermatological Association, Inc., Boca Raton Hotel, Boca Raton, Fla., Apr. 8-12. Dr. Wiley M. Sams, 308 Ingraham Bldg., Miami 32, Fla., Secretary.

American Physiological Society, Chicago, Apr. 11-15. Ray G. Daggs, D.Sc., 9650 Wisconsin Ave., Washington 14, D. C., Executive Secretary.

American Proctologic Society, Shamrock Hilton Hotel, Houston, Texas, Apr. 25-27. Dr. Norman D. Nigro, 10 Peterboro, Detroit 1, Secretary.

American Public Health Association, Southern Branch, Memphis, Tenn., Apr. 13-15. Dr. L. M. Graves, Shelby County Health Department, Memphis, Tenn., Chairman, Local Arrangements Committee.

American Society for Artificial Internal Organs, Pick-Congress Hotel, Chicago, Apr. 10-11. Dr. Charles K. Kirby, 3400 Spruce St., Philadelphia 4.

American Society of Biological Chemists, Inc., Chicago, Apr. 11-16. Dr. Frank W. Putnam, Dept. of Biochemistry, Univ. of Florida, Gainesville, Secretary.

American Society for Experimental Pathology, Pick-Congress Hotel, Chicago, Apr. 11-15. Dr. J. F. A. McManus, Univ. of Alabama Med. Center, Birmingham, Ala., Executive Secretary.

American Society of Facial Plastic Surgery, Hotel Elysee, New York City, Apr. 6. Dr. Samuel M. Bloom, 123 E. 83d St., New York 28, Secretary.

American Society of Internal Medicine, Sheraton-Palace Hotel, San Francisco, Apr. 1-3. Mr. Robert L. Richards, 350 Post St., San Francisco 8, Executive Director.

American Society for Pharmacology and Experimental Therapeutics, Inc., Chicago, Apr. Dr. Karl H. Beyer Jr., Merck Sharp and Dohme Research Labs., West Point, Pa., Secretary.

American Society for the Study of Sterility, Sheraton-Gibson Hotel, Cincinnati, Apr. 1-3. Dr. Herbert H. Thomas, 920 S. 19th St., Birmingham 5, Ala., Executive Secretary.

American Surgical Association, The Greenbrier, White Sulphur W. Va., Apr. 3-6. Dr. W. A. Altemeier, Cincinnati General Cincinnati 29, Secretary.

Andrew, John A., Clinical Society, Tuskegee Institute, Al Apr. 24-29. Dr. Eugene H. Dibble, Memorial Hospital, Tuskegee tute, Ala., Secretary.

Arkansas Medical Society, Pine Bluff, Apr. 18-20. Mr. Paul C. 218 Kelley Bldg., Fort Smith, Ark., Executive Secretary.

Connecticut State Medical Society, Hamden High School, Apr. 26-28. Dr. William R. Richards, 160 St. Ronan St., New Conn., Secretary.

Eastern Psychiatric Research Association, New York U Medical School, Alumni Hall "B," New York City, April 7. Dr. J. Impastato, 40 Fifth Ave., New York City, Secretary-Treasurer

Florida Medical Association, Robert Meyer Hotel, Jacksonville, 8-12. Mr. W. Harold Parham, 735 Riverside Ave., Jacksonville 3, Executive Director.

Harvey Cushing Society, Fairmont Hotel, San Francisco, Apr. Dr. Edmond J. Morrisey, 450 Sutter St., San Francisco, Chairm

Industrial Medical Association, Rochester, N. Y., Apr. 26-29 Clark D. Bridges, 28 E. Jackson Blvd., Chicago 4, Managing

Iowa State Medical Society, Savery Hotel, Des Moines, Apr. Mr. Donald L. Taylor, 529 36th St., Des Moines 12, Iowa, Exe Director.

Maryland, Medical and Chirurgical Faculty of the State of Alcazar, Baltimore, Apr. 20-22. Mr. John Sargeant, 1211 Baltimore 1, Executive Secretary.

Mid-Central States Orthopaedic Society, Wichita, Kan., Apr. Dr. H. O. Marsh, 3244 E. Douglas, Wichita 8, Kan., Secretary.

Nebraska State Medical Association, Hotel Cornhusker, April 25-28. Mr. M. C. Smith, 1315 Sharp Building, Lincoln 8, Executive Secretary.

North Dakota State Medical Association, Dacotah Hotel, Forks, Apr. 30-May 3. Mr. Lyle A. Limond, Box 1198, Bismarck, Executive Secretary.

North Pacific Society of Neurology and Psychiatry, Ben Franklin Hotel, Seattle, Washington, Apr. 8-9. Dr. Thomas H. H University of Washington, Seattle 5, Secretary-Treasurer.

Society of Head and Neck Surgeons, Sheraton Hotel, Philade Apr. 18-19. Dr. Harry W. Southwick, 30 N. Michigan Ave., Chica Secretary-Treasurer.

Society of Neurological Surgeons, Olympic Hotel, Seattle, April Dr. Guy L. Odom, Duke University Center, Durham, N. C., Secr

Southeastern Dermatological Association, Nashville, Tenn., 30-May 1. Dr. Robert N. Buchanan Jr., 706 Church St., Nash Tenn., Organizing Physician.

Tennessee State Medical Association, The Maxwell House, Nash Apr. 10-13. Mr. Jack E. Ballentine, 112 Louise Ave., Nashville 5, Executive Director.

Texas Medical Association, Hotel Texas, Fort Worth, Apr. 9-12. C. Lincoln Williston, 1801 N. Lamar Blvd., Austin, Texas, Exe Secretary.

May

Academy of Psychoanalysis, Hotel Claridge, Atlantic City, N. J., 7-8. Dr. Joseph H. Merin, 125 E. 65th St., New York 21, Secretar

Aerospace Medical Association, Americana Hotel, Bal Harbour, May 9-11. Dr. William J. Kennard, Aerospace Medical Associa Washington Natl. Airport, Washington 1, D. C., Secretary-Treasur

American Association for Cleft Palate Rehabilitation, B Palace Hotel, Denver, May 12-14. D. C. Spriestersbach, Ph.D., versity Hospitals, Iowa City, Iowa, Secretary-Treasurer.

American Association of Genito-Urinary Surgeons, Dearborn Dearborn, Mich., May 11-13. Dr. William J. Engel, 2020 E. 93rd Cleveland 6, Secretary.

American Association on Mental Deficiency, Lord Baltimore H Baltimore, May 16-21. Mr. Neil A. Dayton, P. O. Box 51, Mans Depot, Conn., Executive Secretary-Treasurer.

American Association of Plastic Surgeons, Milwaukee Inn, Milwau May 17-20. Dr. Thomas D. Cronin, 6615 Travis St., Houston 25, T Secretary.

American Association for Thoracic Surgery, Deauville Hotel, M Beach, Fla., May 11-13. Dr. Hiram T. Langston, 7730 Carondelet A St. Louis 5, Secretary.

American College of Cardiology, Indianapolis, May. Dr. Pl Reichert, 2709 Empire State Bldg., New York 1, Executive Direc

American Federation for Clinical Research, Chalfonte-Haddon Atlantic City, N. J., May 1. Mr. James E. Bryan, 250 W. 57th St., York 19, Executive Secretary.

American Gynecological Society, Williamsburg Inn, Williamsburg, May 30-June 1. Dr. Andrew A. Marchetti, Georgetown Univ. H Washington 7, D. C., Secretary.

American Ophthalmological Society, The Broadmoor, Colo Springs, Colo., May 16-18. Dr. Maynard C. Wheeler, 30 W. 59th New York 19, Secretary.

American Orthopaedic Association, The Homestead, Hot Springs, May 30-June 2. Dr. Lee Ramsay Straub, 535 E. 70 St., New York Secretary.

American Pediatric Society, New Ocean House, Swampscott, M May 5-6. Dr. Aims C. McGuinness, 2800 Quebec St., N. W., Washing 8, D. C., Secretary-Treasurer.

American Psychiatric Association, Inc., Hotel Traymore, Atlantic C N. J., May 9-13. Dr. C. H. Hardin Branch, 156 Westminster Ave., Lake City 15, Utah, Secretary.

American Psychoanalytic Association, Chalfonte-Haddon Hall, At tic City, N. J., May 6-9. Mrs. Helen Fischer, One E. 57th St., New Y 22, Acting Executive Secretary.

American Society for Clinical Investigation, Haddon Hall, Atla City, N. J., May 1-2. Dr. Saul J. Farber, N. Y. U. College of Medici 550 First Ave., New York 16, Secretary.

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